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CORONARY OCCLUSION*

ERNEST SCOTT AND MARY K. HELZ

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The terms "coronary occlusion" and "cardiac infarction" have, within very recent years, become familiar terms in medical literature and most of us are of the impression that this disease involving the coronary arteries and the cardiac muscle is a new condition that has arisen among us. If we will take time to investigate, however, we may find very complete descriptions of these changes in the literature of almost one hundred years ago.

Wearn[33] cites a case from the works of William Harvey published in 1845 in which a fairly accurate description of the clinical symptoms are presented. The record of the autopsy states that

> "We found the wall of the left ventricle ruptured, having a vent in it of the size sufficient to almost admit any of my fingers although the wall itself appeared thick and strong; this laceration had apparently been caused by an impediment to the passage of the blood from the left ventricle into the arteries.

John Lindsay Stevans[27] in 1887 introduced his remarks by stating that

> The conditions of the heart wall (especially fibrous transformation) have long been described by special observers, but it is only of recent years that what appears to be, in most cases, their true pathological significance has been hinted at.

This same author quotes Dr. W. T. Gairdner who, in 1854, reported a case of "ossification of the coronary arteries, with tendinous degeneration of the heart muscle." Many other references are cited by this author, who in his own discussion hinted at the acute conditions as "infarctions" and suggested that the coronary vessels played some part in the condition.

* Read before the Ninth Annual Convention of the American Society of Clinical Pathologists, Detroit, Michigan, June 20–23, 1930.

In this country Dock[7] was the first to attempt the diagnosis of infarctions of the heart prior to its recognition at the postmortem, From this time on through the discussion of the subject by Osler,[24] Wearn, Levin,[21] Herrick[13] and many others, the relationship of the clinical manifestations and the accompanying pathology have become well understood.

The study of the pathology of cardiac infarctions leads to the necessity for a better understanding of the normal circulation of the coronary arteries, and in 1921 Louis Gross[11] published his monograph upon the "Blood Supply of the Heart," in which by new methods and better technique he was able to establish definitely the area of distribution of the coronary arteries and their main branches, the abundance of the capillary circulation, the free anastomosis between the capillaries and pre-capillary vessels, the exchange of blood not only between the branches of the same main artery but also between the right and the left coronary arteries. He further demonstrated the areas of over-lapping in the blood supply in different areas of the heart, the anastomosis of the vessels of the epicardial fat and other adjacent vessels with the coronaries, and that anastomosis between the coronary vessels increases with age.

In the distribution of the coronary vessels there are three areas in which the finer branches overlap, such areas receiving their supply from one or the other artery depending upon the pressure at any given time. Kugel[17] has demonstrated the constant presence in fifty human hearts of the large anastomotic artery, first described by Kugel and Gross, passing through the auricular wall and the interauricular septum which joins the left and right coronary arteries. He has named this the arteria anastomotica auricularis magna. Oberhelman and LeCount,[23] by injection methods followed by roentgenograms, were able to demonstrate that in a few hearts no anastomosis exists. In a second group of normal hearts there was a rapid and complete filling of both coronary arteries following the injection of either one. In a third group, in which there were extensive myocardial changes and an advanced coronary sclerosis, there was shown an abundant anastomosis. These authors suggest two factors concerned with the

results of coronary sclerosis; first, the considerable difference in the anastomosis normally existing between the coronary vessels, and second, the time element (whether occlusion has taken place slowly enough that collateral circulation may be established). In a series of experiments conducted in this laboratory it was found that, following the injection of normal saline into either coronary vessel at a pressure of 100 mm. mercury, 1–2 per cent of the fluid was collected from the canula in the opposite coronary orifice.

Gross and Wearn[32] by means of injecting colored fluid into the coronary vessels, have been able to demonstrate an unusually abundant capillary circulation in the normal heart muscle. Wearn[31] was able to prove a capillary for practically every fiber of the ventricle walls and the papillary muscle, though a less abundant supply in the auricle and Purkinje system. This abundance of the capillary circulation can in some measure be realized when the cast of the coronary vessel is obtained by the celloidin injection and corrosion method. Here an extremely fine meshwork of capillaries can be seen so closely packed together that there seems that no space is left for the muscle fibers. Such a cast of the heart vessels also demonstrates the course and distribution of the branches showing the acute angle at which the branches of the left coronary artery leaves the vessel to pierce the muscle.

The Thebesian vessels since their very early description by Vieussens[30] in 1706 and by Thebesius[29] two years later, have created great interest and much difference of opinion as to their function and distribution. Within more recent years Pratt,[25] Crainicanu,[6] Wearn,[31] Grant and Viko[10] have continued these investigations. Pratt first succeeded in demonstrating that it was possible to maintain the beating of the heart by perfusing blood through the Thebesian vessels. Crainicanu observed that salt solution perfused through the coronary arteries after the canulation of the various openings of the heart, the aorta, the pulmonary vein, coronary veins, coronary sinus, and the auricles, that most of the solution escaped into the chambers of the heart and that only a small amount escaped through the coronary sinus. Wearn

in extending these observations, noted that as much as 90 per cent of the fluid introduced into the coronary orifices escaped through the cavities via the Thebesian vessels. He was also able in this manner and by serial sections of the heart to demonstrate connections between capillaries and the Thebesian vessels, and a direct connection between the coronary arteries and the chambers of the heart via the Thebesian vessels.

Grant and Viko, by injections of chrom yellow gelatin and celloidin of varying viscosities into the coronary arteries and also into the Thebesian vessels through their opening in the endocardium, and later by either clearing or digesting the muscle, describe three main types of vessels arising from Thebesian foramina:

1. Vessels forming "trees" and ramifying in the endocardium and the immediately underlying vessels.
2. Channels uniting neighboring foramina and anastomosis between adjacent "trees."
3 Vessels connecting the Thebesian "true" with the coronary veins, and also direct communication of coronary vein and the ventricle.

They conclude their report with the positive statement that the Thebesian vessels communicate with the coronary arteries only through the capillaries.

This brief review of the coronary circulation indicates that the question of the heart's nourishment has occupied the attention of medical investigators from the dawn of anatomical study, and that while much has been learned, the entire mechanism through which the myocardium is fed is still in doubt. This has recently been brought to attention by the report of Leary and Wearn[18] who report two cases of complete closure of the orifices of both the left and right coronary arteries by the thickening of the aortic wall from a syphilitic aortitis, and in our own laboratory there is at present a similar case in which both coronary orifices are so completely closed that no fluid can be forced through them.

Again after such a review of the anatomical peculiarities of the heart's circulation, the question unavoidably asked is why should there be infarcts at all in an organ with such free and abundant

anastomosis between its arteries and in which even the complete closure of one or both branches of its usual sources of supply has been shown without seriously impairing the function of the organ. As an explanation for the question Pratt has postulated the presence of "functional endarteries" or areas in which the resistance is greater than the surrounding pressure. Hirsch and Spalteholz[15] have shown experimentally that the area of infarction is always smaller than the area supplied by the affected vessel, when however, the blood pressure was lowered or poorer in quality the infarct included the entire area of the vessel's supply. He believes that the continuous functioning of the heart, the structure of the vessels and the heart strength all bear a definite relationship to cardiac infarction. In this consideration it must be again noted that the age of the individual, the size of the vessel affected, and the rapidity with which occlusion occurs are matters of utmost importance. For if obliteration is gradual and the circulation good, anastomosis and collateral circulation may be sufficient to maintain the life of the areas involved. Such an abundant collateral circulation may be established that the myocardium maintains its normal appearance and function even when arteries of fair size are closed. Such cases are recorded by Gross and Galli.[8] If, on the other hand, the circulation is partially cut off, it may still be sufficient to maintain the life of the fibrous tissue or stroma of the part, while the more delicate muscle cells will degenerate or disappear through atrophy.

With sudden closure of a large artery there is not time for the establishment of any adequate collateral circulation and the entire area quickly becomes necrotic (myomylaciae cordis).

The deciding factors in the amount and kind of infarction in the heart muscle are the size of the vessel, the rapidity with which occlusion occurs, the condition of the general circulation, and the age of the individual.

The most common age at which coronary disease manifests itself clinically corresponds with that at which it is observed at the autopsy. Herrick and Nuzum[14] note that 82 per cent of cases dying of coronary disease fall in the age range of 40–70 years, while 44 per cent come between 50–60 years. Barker[4] finds the

average age about 54 years with the individual usually over 45. Levine[20] finds the disease mostly in men 55 or over. The average age of Allen's[2] cases is 55.4 years. Cases accompanied by a syphilitic process fall in the earlier age limits. These seem to be 35–55 years on the average. All other cases fall in the upper range averaging around 50–60 years.

All writers agreed that men are more often affected than women, but the earlier idea expressed by Osler[24] that the upper social stratum is predisposed, is being corrected as more cases are studied. Wearn and Levine both cite many cases from the lower levels of society, and in our own series of 36 cases there were two ministers, one physician, one business man, one woman of high social standing; the remaining 31 are classed as common laborers and housewives from the poorer class.

The relation of coronary disease to syphilis is a much debated question. According to Levine[19] syphilis is apparently not an etiological factor in acute cardiac upsets. In Thayer's[28] twenty-four cases of angina pectoris, four showed luetic aortitis only, while five showed luetic aortitis and coronary disease. Levine cites five cases of coronary occlusion, one of which was luetic. Allen collected 371 cases of coronary disease from 1000 consecutive autopsies. Of these, thirteen cases (3.5 per cent), showed some evidence of syphilis of the coronaries "*at or near the orifice.*" Seven of his ninety-seven cases which showed narrowing or blocking of the coronary lumen, belonged in this luetic class, and eleven of the fifty-eight cases of coronary occlusion with sudden death showed this type of syphilitic process.

From the author's description of these cases, it seems that the syphilitic process in the aorta, either extends for a short distance into the orifice of the artery, or the proliferation in the wall of the aorta itself in the region of the sinus of Valsalva mechanically occludes the coronary orifice. These two modes of occlusion are apparently the only ones described in literature directly attributed to syphilis, there being no reference to a true syphilitic degeneration of the walls of the coronary vessels.

In considering coronary disease and angina pectoris care must be taken to distinguish between angina-like pain and true an-

gina.[1] Acute coronary obstruction is often accompanied by severe pain similar to angina. However, there are a goodly number of cases on record in which the typical attacks of angina are described. Some suffer repeated attacks in one of which they die, and at autopsy an acute coronary obstruction can be demonstrated. In other cases there is but one typical anginal attack during which the patient dies. Autopsy in some of these cases also reveals an acute cardiac infarction. Herrick mentions several such cases. Mackenzie,[22] in his work on angina, notices often a diminished blood supply to the myocardium, this being caused in a few cases by aortitis, but most often by coronary disease. He suggests that the pain might be due to a too great burden placed upon the weakened myocardium. Gilbert[9] sees coronary disease often associated with angina pectoris but considers it by no means a causative factor. Albutt[3] on the other hand, believes coronary occlusion has nothing to do with angina pectoris.

In the literature reviewed no direct mention is made of the relation of coronary disease to hypertension, though Levine, Hamburger[12] and many others note enlarged hearts in these patients. Wearn could not establish a direct relationship between the two conditions though they were often found associated. It is therefore interesting to note that in five of the present series hypertension was specifically diagnosed. The lack of symptoms and the suddenness of many deaths in coronary occlusion probably account for the scarcity of data on these attendant conditions, many of these patients never consulting a physician until in the throes of the terminal attack.

Again general arteriosclerosis is an attendant condition which has been seldom mentioned in the discussions of coronary disease, yet its relationship to this condition was indicated by Stevens as early as 1887. The frequency with which it occurred in the present series (44 per cent) would indicate that this condition should be given greater consideration in the etiology of the disease.

In Allen's 371 cases of coronary disease, sudden death from coronary occlusion occurred in only 58 cases. Such occlusion may

take place by several different methods, the most common being that of thrombosis. Any pathological process which tends to roughen the inner surface of a vessel predisposes to thrombus formation. According to Allen atheroma is the commonest of such lesions. An associated calcification complicates the picture in many instances. An arteriosclerotic process with or without calcification also predisposes to thrombus formation. These degenerative processes are quite often diffuse throughout the coronary system, but as Wearn, Allen, and others have pointed out, and as is indicated in the present series, the actual thrombosis occurs in the great majority of cases in the descending branch of the left coronary artery. Syphilitic lesions are proliferative in character and, occurring at the base of the aorta, tend to obliterate the vessel orifice. This type of closure is so gradual that an acute infarction rarely occurs. Albutt cites several such instances of almost complete occlusion of the coronaries. Leary and Wearn's two cases of complete occlusion of both coronary orifices by a syphilitic aortitis and our own similar case have already been referred to.

Occlusion may also be due to an embolus although this does not presuppose coronary disease. The embolus may be paradoxial or may originate in the left heart itself. In one of the cases in the present series the embolus arose from a thrombus in the right femoral vein and reached the left coronary by way of a patent foramen ovale. In another, there was an embolus in the left coronary and a patent foramen ovale, but the origin of the embolus could not be determined. In a third case the embolus arose from a clot in an aneurysm of the ascending aorta.

In order that there may be a definite understanding of the microscopic changes in coronary disease, we have adopted the classification followed by Allen which coincides with our views on the subject. His division is that of (1) atheroma, (2) arteriosclerosis, (3) calcification, and (4) syphilis.

The atheroma originates as an inflammatory process in the deep layers of the intima, and later, becoming fibrous, it produces nodular encroachments upon the lumen. This disease in the coronaries is quite comparable to atheroma of the aorta. It is rather prone to calcereous degeneration in its later stages.

Arteriosclerosis is a diffuse process probably originating in the medial and sub-intimal layers. It leads to a diffuse fibrosis with thickening of the media, sometimes extending into the intima. This is also prone to calcereous degeneration.

While syphilitic aortitis is a common manifestation of syphilis, the disease seems rarely to attack the coronaries. A syphilitic mesaortitis may encroach on the lumen of the coronaries at their orifices or as has been stated before, may extend a short distance into the coronary. However, in the present series, there is one case presenting proliferation and fibrosis of the intima accompanied by a round cell infiltration which seems to originate in the adventitia and extend into the media. The appearance is quite similar to the accepted picture of syphilitic aortitis and syphilis of the medium sized vessels as described by Saphir.[26]

The alterations in circulation due to coronary obstruction can be divided into two main classifications, namely those following sudden obstruction and those due to gradual closure. An acute infarction follows sudden obstruction. Oberhelman and LeCount found that in a few hearts there was no vascular anastomosis. As they also pointed out, a sudden occlusion, especially of a fairly large branch, does not give time for functional anastomosis and myocardial ischaemia is the result. In the event of this too sudden interference, death ensues. Gross points out that functional anastomosis may carry enough blood to proliferate and nourish fibrous tissue and thus conserve the life of the patient, while it is not sufficient to the needs of highly specialized muscle.

In sudden occlusion the microscopic picture in the myocardium is one of acute infarction. Karsner and Dwyer[16] in their experiments upon dogs found that by surgically ligating a coronary artery, infarctions could be produced. These dogs were allowed to live for varying lengths of time and then the heart removed for examination. By knowing the exact age of the infarct, the progressive myocardial changes could be studies. Thus they have a complete myocardial picture from the occlusion until complete healing by fibrosis. Buckley[5] finds cardiac infarction responsible for most cases of spontaneous rupture of the heart.

However, this is not the most common end result of infarction. A great many infarctions end in fibrosis. This is especially true when smaller areas are affected.

The most common type of vascular obstruction in the heart is that which takes place gradually. Here the collateral circulation plays a great part because we see no acute infarction. The new circulation, unable to carry enough blood for all the myocardium, can support the growth of connective tissue. Mackenzie, Wearn, Hamburger, and Allen all agree that fibrosis is the usual result of gradual closure of the coronary arteries. Mackenzie goes on to say that if this fibrosis is extensive enough, death may follow from progressive myocardial failure, the heart muscle being unable to compensate for the extra strain placed upon it. In our experience the most common picture is an acute infarction superimposed upon a chronic fibrosis. The coronary picture is one of a narrowed lumen suddenly blocked by a thrombus. A syphilitic process which gradually obstructs the coronary orifice seems to lead to fibrosis less often, according to Allen.

ANALYSIS OF THIRTY-SIX CASES OF CORONARY OCCLUSION

Age:	
Average age	57.5 years
Average age of syphilitics	51.6 years
Sex:	
Males	32
Females	4
Race:	
White	31
Black	5
Associated clinical findings:	
Angina pectoris diagnosed	4
Hypertension diagnosed	5
Hypertrophy and dilatation of heart	3
Cerebral hemorrhage	3
Sudden death	22
Death in 10 to 12 hours	2
Slow death	7
Manner of death unknown	5
Pain	11

Myocardium:	
Acute infarction superimposed upon fibrosis	16
Fibrosis	5
Acute infarction	8
Acute infarction with rupture	2
Vascular disease:	
General sclerosis	17
Syphilitic aorta	16
Atheromatous aorta	3
Arteriosclerotic aorta	11
No aortic disease noted	6
Coronary arteries:	
Occlusion main branch left coronary	11
Occlusion bifurcation left coronary	2
Occlusion descending branch left coronary	15
Occlusion intermuscular branches left descending coronary	2
Occlusion right coronary	5
Occlusion both coronaries	1
Manner of final occlusion:	
Thrombus	29
Embolus	3
Syphilis	1
Manner of occlusion unknown	3
Coronary disease:	
Arteriosclerosis	16
Atheroma	1
Syphilis	3
Arteriosclerosis and calcification	7
Atheroma and calcification	5
General syphilis:	
A diagnosis of syphilis was possible in	17
A doubtful diagnosis in	1

SUMMARY

1. In distinction from other series of cases the present series showed seventeen (47.2 per cent) syphilitics.

2. Virtually all cases in the series were accompanied by a general vascular disease.

3. In thirty of the thirty six cases the left coronary was occluded.

4. The right coronary was occluded in only five cases.

5. In one case both coronaries were completely occluded.

6. The most common coronary lesion was arteriosclerosis with superimposed thrombosis.

7. The most common myocardial lesion was an acute infarction superimposed upon chronic fibrosis.

8. The most frequent victim of coronary occlusion was a white male 50–60 years of age.

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THE ELECTROMOTIVE THERMOMETER

An Instrument and a Method for Measuring Intramural, Intravenous, Superficial and Cavity Temperatures*

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Seebeck, of Berlin, in 1821, discovered that if, in a circuit made of two different metals, one junction is hotter than the other, an electromotive force is developed which causes an electric current. This electromotive force is generally very small compared with ordinary single unit batteries and the like, which have voltages of from 1 volt to 2 volts. For example, in a circuit containing copper and iron (hence two junctions), when one junction is at 100°C. and the other junction is at 0°C. the electromotive force is of the order of a thousandth of a volt. This voltage, however, causes an electric current to flow from copper to iron at the hotter junction and from iron to copper at the colder one when the electric circuit is closed.

In order to obtain larger electromotive forces, pairs of metals have been combined in series to form thermopiles. The form devised by Nobili and used by Melloni in his researches on heat radiation consisted of alternate strips of antimony and bismuth which were insulated carefully from each other, except at the junctions, where they were soldered together. These metals were chosen because they gave a large electromotive force which acted from bismuth to antimony at the hot junction and from antimony to bismuth at the cold junction.

I do not know to whom is due the credit for the initial use of thermocouples and thermopiles in obtaining measurements on

* Read before the Ninth Annual Convention of the American Society of Clinical Pathologists, Detroit, Michigan, June 20–23, 1930.

the temperatures in various parts of the human body. The first reference I have been able to find is a paper by Lombard.[11] Lombard employed thermopiles of eight pairs of bismuth and of an alloy of antimony and zinc. In the same year and journal, Allbutt[2] published a short paper on the clinical thermopile. He used thermopiles of bismuth and antimony. He gave some reports of his clinical observations and wrote by way of conclusion: "Perhaps the most valuable results I have obtained are the relations between superficial and internal heat."

Passing over the rather sparse medical literature dealing with thermocouples and thermopiles for the determination of the temperatures of body surfaces and tissues from 1875 to 1915, I shall call attention briefly to some of the more recent investigations.

Holding[10] described his thermocouple thermometer as an instrument "for the exact measurement of temperature in living tissues for use in coagulation surgical procedures." He employed a potentiometric method for reading the electromotive forces developed by the heat of the tissues, particularly in procedures involving diathermy and electrocoagulation.

Crile[7,8,9] and his collaborators made a series of thermo-electric studies of variations in temperature in animal tissues, the effects of anesthesia, electrical stimulation, abdominal trauma, exposure of viscera, excision of organs, acid, alkali, strychnine and epinephrine.

Wagner[13] described the construction and use of thermoneedles for measuring the temperature of deep lying organs and used such thermocouples in tumors, muscles and the like.

Bazett and McGlone[4] employed couples of constantan and iron for the measurement of superficial temperatures and used steel needles with constantan for dermal and subcutaneous measurements. One of the junctions in their portable apparatus was inserted in an insulated (thermos) flask of a capacity of one pint and filled with paraffin oil at room temperature. They used a galvanometer of the double pivoted movable coil type (Weston, Model 440), of internal resistance of 3.5 ohms, period of 2.3 seconds and deflections indicating 2.2 microamperes in each division. The sensitivity of their ensemble was between 0.6 and

0.8°C. for each division of the scale, insuring an accuracy of about 0.2°C. in the estimation of temperature by their thermoelectric method.

In various topographical surveys of the temperatures of the body at numerous (forty-seven) cutaneous situations, Benedict,[4] and Benedict, Koropatchinsky and Finn[5] used thermocouples of constantan and iron, a thermostat for maintaining one junction at a constant temperature (32°C.) and a portable galvanometer (Leeds and Northrup number 2400), with a sensitivity of 20 microvolts, which indicated a change of temperature of practically 0.04°C. for each millimeter of deflection of the galvanometer. There are many valuable details concerning construction of apparatus and methods of obtaining temperatures in these papers by Benedict and his collaborators.

Clark[6] designed and built a sensitive apparatus (reading to 0.01° C.) for the measurement of intravenous temperatures employing thermocouples of constantan and copper. He made a thermostat consisting of a double flask or tubes of pyrex glass, the space between being filled with mercury which served both as the constant temperature bath and, by the change of volume of the mercury and subsequent change of level in the capillary tubes attached to the apparatus, as the regulator of the temperature. The thermostatic apparatus which I have used in the electromotive thermometer is a modification of the device of Clark.

THE FUNDAMENTAL PRINCIPLE OF THE ELECTROMOTIVE THERMOMETER

The electromotive thermometer is based on the physical principle that an electromotive force (voltage) is developed in a circuit which consists of junctions of two different metals, such as constantan and copper, when one junction or thermocouple is at a higher temperature than the other junction. If a galvanometer is included in this circuit, the electromotive force developed by reason of the differences in temperature of the two junctions will cause an electrical current to flow through the galvanometer. If, then, the difference between the temperatures of the two junctions is known, it is possible to calibrate or to convert the galvano-

metric deflections into equivalent thermal readings. Having calibrated the deflections of the galvanometer in equivalent thermal readings, any of the various thermocouples with which the apparatus is equipped may be applied to or inserted into the body and the temperature read from the calibrated scale, provided the value of the resistance in each of the thermocouple circuits is the same. In passing, it should be noted that the thermocouple, whether bare or inserted in a needle or other enclosing capsule (as in the rectal or gastric thermocouple) should remove as little heat as possible from the surrounding tissue if it is to indicate accurately the temperature of the tissue. In many instances it is difficult to accomplish this: therefore, thermocouples in some cases will be more significant as indicators of the change of temperature produced or induced by various clinical or surgical procedures.

THE ELECTROMOTIVE THERMOMETER

The ensemble of apparatus consists essentially of two parts: (1) the thermostat and heating circuit so arranged that one set of junctions (constantan, copper) or, in the lastest type of instrument, one common junction, can be kept at a constant temperature, and (2) the various types of thermocouples for use in the determination of intramural, intravenous, superficial and cavity temperatures. The galvanometer, used as the instrument for the measurement of the difference in electromotive forces of the two junctions (as for example, the junction at a constant temperature in the thermostat and the junction applied to a given area on the skin) may be of any degree of sensitivity desired, dependent on the distance of the scale on which the deflections are read and the degree of accuracy of measurements desired.

The thermostat

This is essentially a modification of the double container or flask of pyrex glass designed by Clark. A photograph of the thermostatic flask which is used in the apparatus is shown in figure 1. It is shown also in cross section as a portion of figure 2. The length of the double flask portion is 7 inches; the

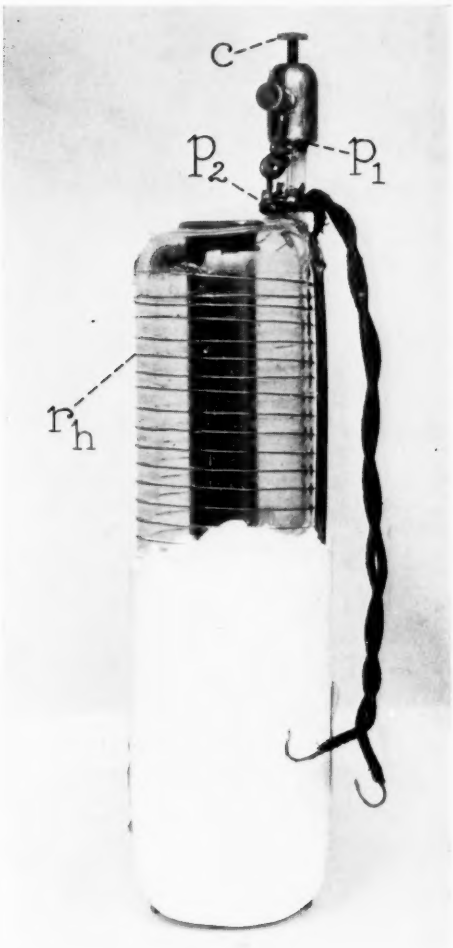

FIG. 1. THE PYREX DOUBLE FLASK OR THERMOSTAT

p_1 and p_2, platinum wires which, with mercury, form the thermostatic control; c, the adjustable screw to which is attached one platinum wire and which serves as the regulator of the value of the constant temperature of the thermostat; r_h, the resistance which constitutes the electrical heating system of the thermostat.

diameter of the outer tube is 2 inches. In the center of this outer flask there is sealed a second tube, about 1 inch in diameter. At

the top of this double flask, and toward the outer edge, there is sealed a piece of pyrex capillary tubing of 1.5 to 2 mm. internal bore and 1 inch in length. The upper end of this capillary tube is flared or cupped. Over the top of this cup is fitted a metallic cap and screw (fig. 2, *c*). At the end of the screw is a small platinum wire (fig. 2, *p*) which makes contact with the mercury

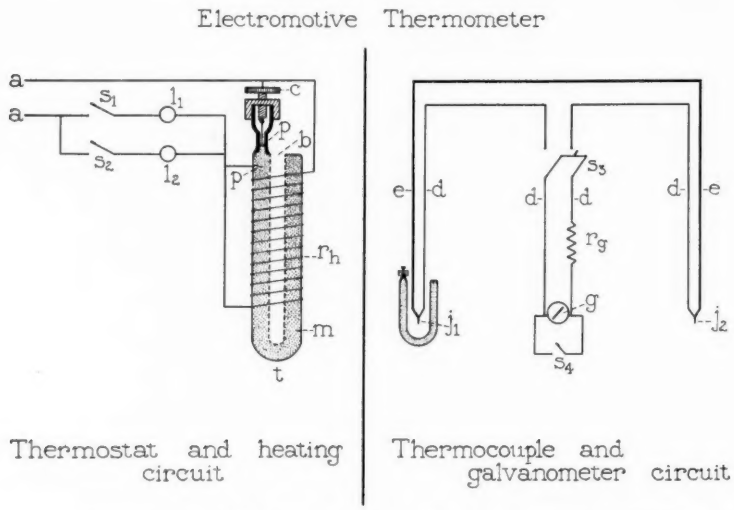

FIG. 2. DIAGRAMMATIC SKETCHES OF THE ELECTROMOTIVE THERMOMETER

Left-hand diagram: *a–a*, 110 volt circuit; s_1 and s_2, switches for inserting auxiliary resistances (incandescent lamp bulbs) l_1 and l_2 in the circuit; *c*, adjustable screw; *p–p*, platinum wires which, with mercury, form the thermostatic control; *b*, inner tube of thermostat which carries one set of thermojunctions; *m*, mercury; r_h, resistance for heating thermostat.

Right-hand diagram: j_1, j_2, thermojunctions of copper, *d*, and constantan, *e*; r_g, auxiliary resistance in galvanometric system; *g*, galvanometer; s_3, switch for including the galvanometer in the thermo-electric circuit; s_4, shunt to damp the galvanometer quickly.

(fig. 2, *m*) as it expands under the heat derived from the electrical heating of the thermostat (fig. 2, r_h). By means of the adjustment of the screw (fig. 2, *c*) the temperature of the thermostat may be set at any value desired. The thermostat proper (fig. 2, *t*) is wound with about 15 feet of number 24 "advance" wire (Driver-Harris Co., Newark, New Jersey) and has a resistance

of about 10 ohms. It is then coated with plaster of paris to a depth of about $\frac{1}{4}$ inch and is finally inserted with proper insulation in the metallic case which is furnished with thermos bottles. The glass portions of the thermostat may be obtained from the Central Scientific Company, Chicago.

The heating circuit

The thermostat is electrically connected to the usual 110 volt lighting circuit. Two ordinary incandescent lamps (or more if desired) are arranged in parallel. One or both of these lamps may be included in the circuit by means of switches (fig. 2, s_1 and s_2). Initially, both switches are closed so that the temperature of the mercury in the thermostat and hence the temperature of the oil in the inner tube (fig. 2, *b*) may be raised to the desired value as quickly as possible. If the screw (fig. 2, *c*) has been set by previous trial to cause the heating circuit to be "off" at a temperature of 40°C., it is possible to insert a Centigrade thermometer accurately calibrated in tenths of a degree (range to 50°C.) in the inner flask (fig. 2, *b*) and, when the temperature indicated on this thermometer rises to within a few degrees of 40°C., the switch (fig. 2, s_2) can be opened and the temperature of the thermostat allowed to come more slowly to its fixed or constant value. The temperature of the thermostat can be kept constant to within less than 0.05°C. if redistilled mercury is used in filling the double-flask container. As will be seen by reference to figure 2 (left-hand portion), the electric current from the main supply passes through the resistance r_h until such time as the mercury has been heated sufficiently and has expanded to make contact with the platinum wire (*p* in upper right-hand portion of fig. 2) attached to the adjusting screw (fig. 2, *c*). When this contact occurs, the electrical current does not pass through the resistance r_h, but follows the path a–c–p–p–l_1–s_1–a (fig. 2). If arcing occurs at the break of the contact of the platinum point of the adjusting screw (fig. 2, *c*), a satisfactory remedy will be found in the employment of condensers (such as telephone condensers) placed across the mercury-platinum "make and break" points.

The thermostat and heating circuit

Figure 3 is a photograph of the arrangement of lamps (fig. 3, l_1 and l_2) and the situation of the thermostatic control in the electromotive thermometer. The current, after passing through the lamp or lamps in the circuit, goes through the resistance wire

FIG. 3. PHOTOGRAPH OF THERMOSTAT AND ELECTRICAL CIRCUIT

l_1 and l_2, lamps; p_1 and p_2, adjustable screw and platinum wires of thermostat; a and b, leads from p_1 and p_2 to main 110 volt circuit.

wound around the pyrex double flask containing the mercury. The points marked a and b (fig. 3) indicate the binding posts to which are fastened wires leading to the two platinum contacts (fig. 3, p_1 and p_2).

The thermocouples

These are made of copper and constantan wires. The copper wire used is well insulated, B and S gauge 27, and consists of

seven number 35 wires, tinned and laid straight. It is commercially sold under the code name "Habitual" (Belden Manufacturing Co., Chicago). The constantan wire is made by the Driver-Harris Company, Newark, New Jersey, and is sold under various trade names, such as "Ideal" and "Climax." A flexible, well insulated wire made of four strands number 35 or 36 is

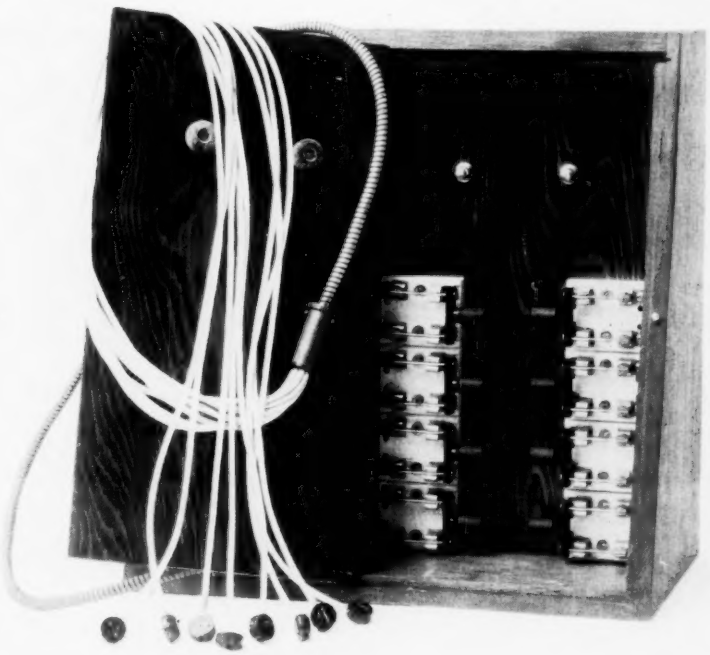

FIG. 4. PHOTOGRAPH OF SKIN THERMOCOUPLES AND SWITCHES CONNECTED TO EACH PAIR OF THERMOCOUPLES RESPECTIVELY

suitable. It is an advantage to use stranded wire of such an alloy, since it is less brittle and less likely to break than the non-stranded type. Also, by using wires of these diameters it is possible thoroughly to interweave and wrap the ends of the copper and constantan wires together for about a quarter of an inch before applying a drop of solder at the tip.

In the earlier models (constructed from 1925 to 1929) one of

each of the various pairs of copper-constantan thermocouples was inserted in the thermostat, and the other junction and wires, forming the second of each pair of thermocouples, were led through several (generally six) feet of rubber tubing of about the same size as the smallest Rehfus tubing (fig. 4). Each pair of thermocouples was connected to the galvanometer in the manner indicated in the right-hand diagram of figure 2. In certain types of experiments (with diathermy), however, some difficulties arose by reason of the fact that the insertion of ten or more thermocouples

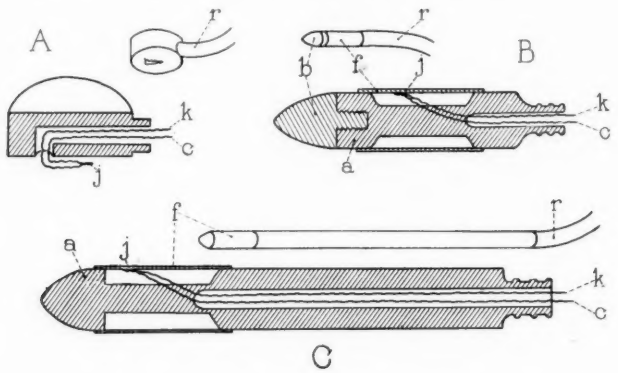

FIG. 5. DIAGRAMS TO SHOW CONSTRUCTION OF CUTANEOUS THERMOCOUPLE *A*, GASTRIC THERMOCOUPLE, *B*, AND RECTAL THERMOCOUPLE, *C*.

k, constantan; *c*, copper; *a*, fiber or hard rubber; *b*, metal cap; *f*, thin copper tubing; *r*, rubber tubing; *j*, thermojunction.

in the inner flask of the thermostat caused these thermocouples to come in contact with each other. This contact was prevented by inserting each thermojunction (in the thermostat) into a small glass tube. The arrangement of switches for enabling the operator to complete the circuit of any desired pair of thermojunctions through the galvanometer, and thereby to get a reading of the temperature indicated by any given thermocouple is shown in figure 4. A group of thermocouples suitable for use in the measurement of cutaneous temperatures is also shown in the same photograph.

Figures 5 and 6 are a series of sketches indicating the manner of construction and housing of thermocouples to be used in ob-

taining superficial, intravenous, intramural, or cavity temperatures. In the measurement of gastric or rectal temperatures it is essential that the thermocouple come nearly in contact with a very thin, small, metallic shell which serves as the container so that it may register as quickly and accurately as possible the temperature of the tissue with which it is in contact. Thermocouples can be made interchangeable also, as for example those used in intravenous, rectal, and gastric measurements, if the copper and constantan leads are fastened respectively to metallic

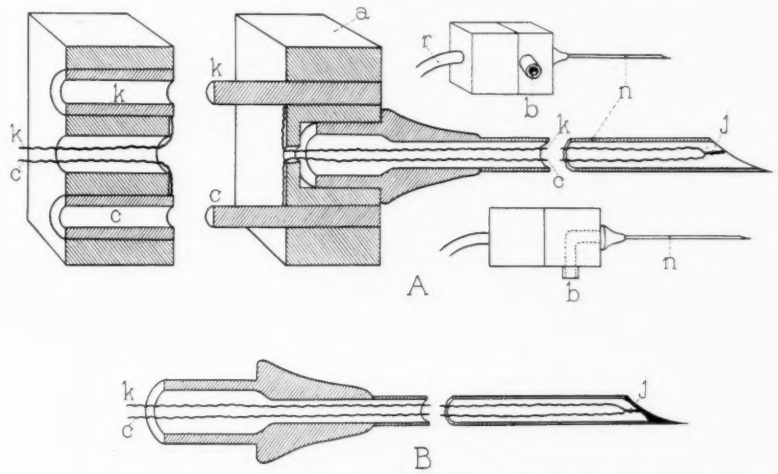

FIG. 6. DIAGRAMS TO SHOW CONSTRUCTION OF INTRAVENOUS THERMOCOUPLE, *A*, AND INTRAMUSCULAR OR INTRAMURAL THERMOCOUPLE, *B*

k, constantan; *c*, copper; *r*, rubber tubing; *b*, attachment for bulb; *n*, needle, and *j*, thermojunction.

bushings of copper and constantan. The attachment containing the thermocouple proper can be conveniently joined by a jack, the constantan lead always being inserted in the bushing of constantan. The essential point to be emphasized is that matters shall be so arranged that two junctions of dissimilar metals occur at two points only; namely, the copper-constantan junction in the thermostat, and the similar junction in the needle or other holder to be inserted into or attached to the body.

The galvanometer

Any galvanometer of the d'Arsonval type, and of sufficient sensitivity, may be used. A Leeds and Northrup type R galvanometer 2500-a has been found satisfactory. If the galvanometer is too sensitive, a resistance of suitable value (fig. 2, *r*) may be inserted in series with it. The external circuit from the thermostat through the switches to the galvanometer, including binding posts, wire terminals, resistances, and so forth, are of copper. All metallic parts in the circuit (fig. 2, *d–d*), or similar circuits, are of copper. In general, I have mounted the galvanometer on one wall of a room in which the instrument is to be used and have used a lamp house with an image of a wire attached to the housing (or the image of the filament of a single filament lamp may be employed) as an indicator of the galvanometric deflection. The scale, calibrated in degrees and fractions thereof, may be fastened to a wall or other support at some distance from the galvanometer. Such a scheme makes the matter of obtaining a long series of readings much easier than the use of the ordinary scale and telescope.

IMPROVED TYPE OF ELECTROMOTIVE THERMOMETER

In the last year the instrument has been improved in several particulars. One thermocouple only is inserted in the thermostat and thus serves as the common junction to each and every pair of thermocouples. The elimination of several thermocouples in the thermostat through the use of a common constantan-copper junction makes it possible to measure temperatures in various parts of the body when diathermy or other high-frequency apparatus is employed in treatment or observational work. From the practical standpoint, also, there is a considerable saving in the time and trouble of making and inserting in the thermostat the sixteen thermocouples which are attached in the latest form of instrument.

Another important improvement lies in the type of switch used to enable the operator to join quickly into the galvanometric circuit any thermocouple desired. The essential details of the

dials and their construction are shown in figure 7. Through the use of constantan and copper rods and ribbon (strips), it has been possible to construct a rotary switch in which all the points of contact on the upper plate (fig. 7, part 1) are of copper. A lower plate of similar construction carries constantan contacts. The copper lead wire of each thermocouple respectively is attached to the appropriate copper terminal in the upper plate, and, in turn, the constantan wires are fastened to the lower plate. The two rotating arms of the dial are made of copper (fig. 7, r_c) and con-

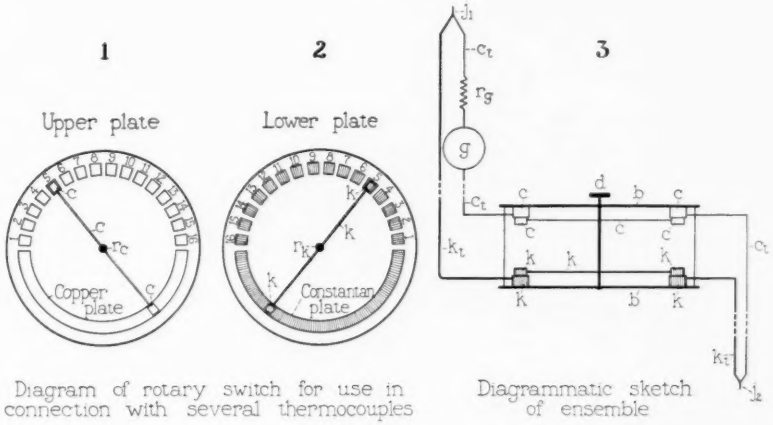

FIG. 7. DIAGRAM OF ROTARY SWITCH AND SKETCH OF ENSEMBLE

c, copper; k, constantan; r_c, rotor arm of copper; r_k, rotor arm of constantan; g, galvanometer; r_g, resistance (copper) in galvanometric circuit; b, b, supporting plates of hard rubber of bakelite, and j_1 and j_2, thermojunctions of copper and constantan.

stantan (fig. 7, r_k) respectively. The upper and lower base plates of the rotary switch are of hard rubber and bakelite. Figure 7 (part 3) shows in diagrammatic form the complete circuit when the rotary switch is set to include any desired thermocouple (for example, number 5) in the galvanometric circuit. Again, it may be pointed out that the galvanometer (fig. 7, g), the auxiliary resistance (fig. 7, r_g), the leads and the wires which form portions of one part of each complete thermocouple unit are of copper. The other portions of the circuits are constantan.

Through his careful construction of instruments, Halstead has eliminated technical difficulties and has made the electromotive thermometer a useful instrument in clinical research and in experimental medicine and biology.

APPLICATIONS OF ELECTROMOTIVE THERMOMETRY

Thermocouples inserted in surgical needles have been used by the writer and his colleagues in a study of the production of fever

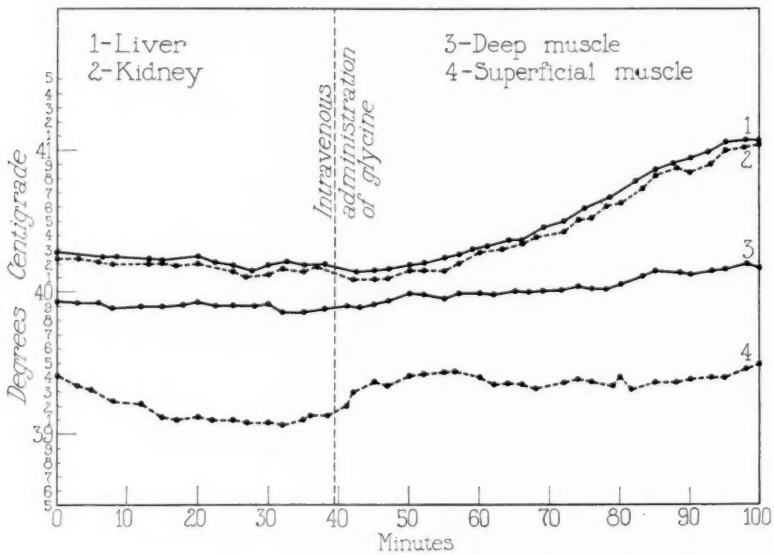

FIG. 8. RECORD OF TEMPERATURES IN THE LIVER, KIDNEY, DEEP MUSCLE AND SUPERFICIAL MUSCLE BEFORE AND AFTER THE ADMINISTRATION OF GLYCINE

in animals by various means. Figure 8 gives a series of readings of the temperatures of the liver, kidney, deep muscle and superficial muscle of an anesthetized animal before and after intravenous administration of 0.5 gm. of glycine for each kilogram of body weight. I shall not present in this article these and other data obtained in these investigations, but I have included figure 8 to indicate the adaptability of the electromotive thermometer to such experiments.

In figure 9 are plotted the readings of temperature obtained on the two great toes with cutaneous thermocouples, the gastric temperatures as obtained through the use of the special gastric thermocouple, and the oral temperature (mercurial thermometer) of a person, after the administration of typhoid vaccine (1,000,000

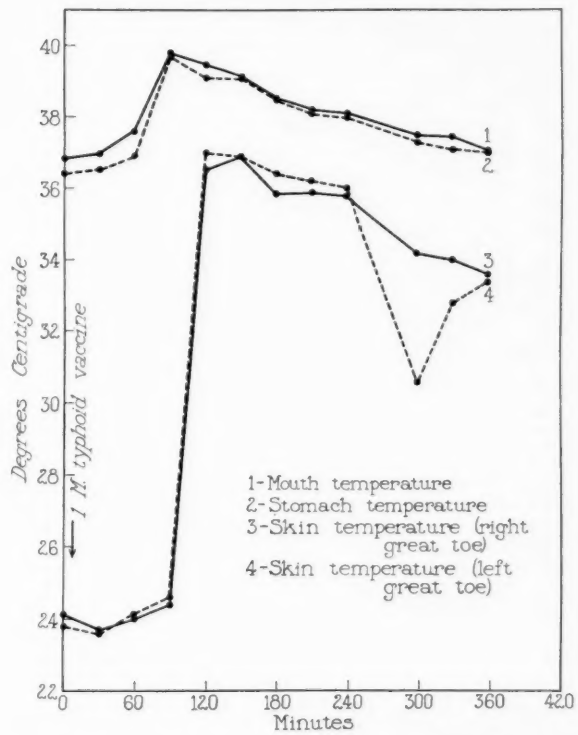

FIG. 9. OBSERVATIONS ON THE CUTANEOUS TEMPERATURE, ORAL TEMPERATURE, AND GASTRIC TEMPERATURE AFTER THE ADMINISTRATION OF TYPHOID VACCINE (1,000,000 *Eberthella typhi*)

Eberthella typhi). The course of the fever, as indicated by superficial and cavity temperatures, is clearly portrayed. The physiologic and clinical significance of such data is reserved for presentation elsewhere.

Extensive clinical calorimetric and thermometric studies have been made by some of my medical colleagues. In these investi-

gations they have made use of the electromotive thermometer and the foot calorimeter previously described by me.[12] Adson and Brown[1] wrote:

Subjects who exhibit vasospastic disturbances are especially prone to have decreased temperature of the skin with marked fluctuations in the involved parts. Under usual environmental conditions, room temperature 24° to 26°C., the surface temperature is low in the hands and feet, ranging from 16° to 25°C. The surface temperature of the extremities of the average normal person varies from 24° to 33°C. In cases of Raynaud's disease, the fluctuations in surface temperature are extreme and constitute an exaggerated response to variations in the environmental temperature. This is shown, not only with determinations of the surface temperature by the thermocouple, but also in variations in the rate of heat elimination as determined by the foot and hand calorimeter. During the stage either of pallor or of cyanosis the surface temperature of the part becomes excessively low and increases with recovery to normal color. As the disease becomes more advanced, there is an increasing tendency for the surface temperature to remain low. The marked vasospastic element present in these cases also is shown in the response of surface temperature and in the rate of heat elimination when systemic fever is induced. For the purpose of studying the range of the vasomotor response, a procedure has been developed which gives information on this point and serves as a useful index in determining the type of case amenable to operative measures. It is particularly valuable in cases of thrombo-angiitis obliterans which are frequently complicated by vasospastic disturbances. One of us (Brown) has devised what we call the "vasomotor or vascular index" which is determined as follows: Nonspecific protein fever is induced by the intravenous injection of triple typoid vaccine, and the surface temperatures of the digits, foot, and hand, are taken simultaneously with the temperature in the mouth, or roughly simultaneously with the temperature in the blood. In all persons, including those who are normal and those with or without vascular disease, after a preliminary drop due to the chill, the temperature in the mouth and on the surface rises. The magnitude of the rise in the temperature of the skin is dependent on (1) the initial temperature of the extremity, (2) the severity of the febrile reaction, and (3) the patency of the arteries. In cases in which the extremities are cold and in cases in which there is considerable vasospasm, the increase in the surface temperature is very great. The index is calculated by determining the rise in the surface temperature and subtracting from that the rise in the temperature of the mouth or blood; this, in degrees Centigrade, constitutes the change in temperature of the skin that is due largely to the shifting of blood that comes from vasomotor changes. This increase, divided by the number of degrees increase in the temperature of the blood, gives a figure which, in simple terms, indicates that for every degree rise in the temperature of the blood there is in the temperature of the skin a

certain number of degrees of rise which is largely of vasomotor origin. In cases of Raynaud's disease, indexes of from 5 to 14 are obtained. In the cases of thrombo-angiitis obliterans with vasospastic disturbances, indexes of 2 to 6 have been found. This index is of practical importance in the selection of cases for operation, as the rise in surface temperature that comes with fever approximates roughy that occurring after a sympathetic ganglionectomy. It also has a certain diagnostic import in differentiating cases in which the diagnosis of a pure vasomotor disturbance and early organic disease of the arteries is not entirely clear. In arteriosclerotic disease of the limbs, the vasomotor indexes are low or zero. To obtain such an index militates against operation on the sympthetic system.

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A NOTE ON THE DISTILLATION OF AMMONIA IN THE FOLIN AND WU METHOD FOR THE DETERMINATION OF UREA IN BLOOD

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A simple modification of the distillation procedure in the Folin and Wu[1] method for the routine determination of urea in blood has proved extremely helpful for our hospitals. The changes proposed resulted from an attempt to overcome the trouble which some workers, particularly students and others of little experience in the laboratories, had encountered with the distillation process of the original method. The principal causes of difficulty were (1) frothing in the distillation tube with the carrying over of some of the contents, (2) sucking back of the distillate, and (3) blowing out of the distillate from the receiving tube by steam as a result of too rapid distillation. Elimination as far as possible of these potential sources of error in the original procedure has met with considerable success.

We have abandoned the use of the loosely fitting rubber stopper on the long arm of the bent glass tubing to hold the 25 cc. graduated receiving test tube* in position. Instead, we place this test tube in a 600 cc. beaker filled with cold water and bring it into place for distillation by raising the beaker so that the end of the glass tubing comes well below the surface of the 0.05 normal hydrochloric acid in the receiving test tube. The beaker is held in position during the distillation by a wooden block of suitable size.

* A graduated test tube is used for convenience if one follows the writer's modification of the Folin-Wu method using the Peebles-Lewis Colorimeter (PEEBLES AND LEWIS, Jour. Am. Med. Assn., **70:** 679, 1918; LEWIS, Jour. Lab. and Clin. Med. In press). If the original Folin-Wu procedure is to be followed, an ordinary test tube with a single graduation at 25 cc. may be used.

Very little change has been made in the technique of the method. A piece of paraffin about three times the size of the head of an ordinary pin is used in place of the two drops of mineral oil to prevent frothing, and two small glass beads instead of a dry pebble are employed to prevent bumping. It is important that the bent glass tubing used in the distillation apparatus should have an inside diameter of from 5 to 6 mm., as some difficulty has been

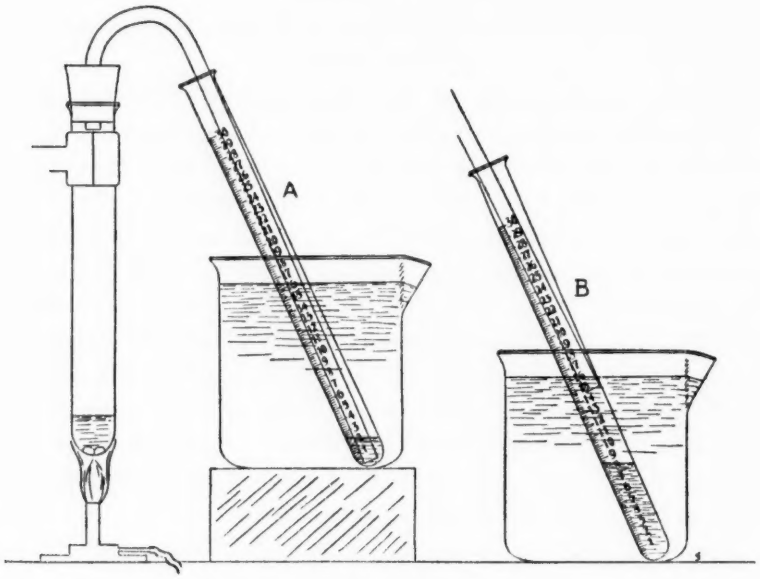

FIG. 1. DIAGRAMMATIC REPRESENTATION OF THE MODIFIED DISTILLATION APPARATUS

A shows position of receiving tube during distillation; *B*, after completion of distillation with the receiving tube lowered by removal of the wooden block.

experienced from a tendency of the distillate to suck back when smaller tubing is used.

Distillation is started over a micro-burner and is continued until from 5 to 6 cc. of water have been distilled into the receiving tube. Then the block is removed and the beaker is lowered to the table top, thereby dropping the graduated test tube so that the end of the glass tubing no longer dips below the surface of

the distillate. Fig. 1 is a diagrammatic illustration of the apparatus used in the distillation.

As the beaker of water keeps the lower end of the distilling tubing and the receiving test tube sufficiently cool to bring about good condensation throughout the distillation, it is not necessary to regulate the rate of distillation to prevent the emission of steam from the receiving tube before the end of three minutes. Irrespective of how rapid the rate may be, all steam will be condensed before reaching the receiving tube. No trouble whatsoever has been experienced from frothing, as mentioned by Watson and White,[2] or from bumping. There is no tendency for the distillate to suck back into the distillation tube. Consequently, after the flame is started, one may do other things about the laboratory and give absolutely no attention to the distillation until it is time to lower the receiving tube.

SUMMARY

1. Certain potential sources of error inherent in the procedure for distillation of ammonia as described by Folin and Wu in their method for the determination of urea in blood have been entirely eliminated through the changes which we have proposed.

2. The revised technique has been used in our laboratories for the past eight years with great satisfaction.

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A METHOD FOR THE DETERMINATION OF BLOOD CHLORIDES USING PALLADIOUS NITRATE AS INDICATOR*

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The use of palladious nitrate as an indicator in the titration of silver nitrate with potassium iodide in the determination of silver was introduced by Schneider[2] who stated that "the stability of palladious iodide is greater than that of ferric sulphocyanate," and that "dilution does not affect the sensitivity of the indicator." The sensitivity and permanency of this indicator suggested the possibility of its use in the determination of the relatively small amounts of chlorides contained in blood.

Numerous methods for the determination of blood chlorides have been reported in the literature. Although accurate results are possible with most of the procedures which have been proposed, the end-points of the titrations are in many instances none too sharp or, in the case of the iodometric methods, can be obtained only by the use of buffer starch indicator solutions, which do not keep well. Consequently, the introduction of palladious nitrate as an indicator in the determination of blood chlorides seemed very well worth an attempt.

PALLADIOUS NITRATE METHOD FOR BLOOD CHLORIDES

Preliminary work having shown that palladious nitrate is sufficiently sensitive to be used satisfactorily as an indicator in the

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† The experimental data presented here are taken from the thesis submitted by Neva L. Binkley to the Graduate School of the University of Colorado, June, 1930, in partial fulfillment of the requirements for the degree Master of Science.

titration of silver nitrate of such low concentrations as are necessary in the determination of blood chlorides, the following method was adopted.

Solutions required

1. Sulphosalicylic acid. A 2 per cent solution.
2. Standard silver nitrate solution (1 cc. = 1.28 mgm. NaCl).

Silver nitrate, C.P.	3.72 grams
Nitric acid, conc	250 cc.
Water to make	1000 cc.

3. Standard potassium iodide solution (2 cc. = 1 cc. Standard $AgNO_3$. Transfer approximately 1.9 gm. of potassium iodide to a liter volumetric flask, dissolve in water, and dilute to volume. Measure 1 cc. of the standard silver nitrate solution, 9 cc. of water, and 0.2 cc. of palladious nitrate indicator into a small Erlenmeyer flask and titrate from a micro-burette with the potassium iodide solution to the first permanent brown color. After checking the titration, adjust the solution by dilution so that exactly 2.03 cc. instead of 2 cc. of the potassium iodide solution will be required to titrate 1 cc. of the standard silver nitrate solution to the brown end-point with palladious nitrate indicator. The extra 0.03 cc. of potassium iodide solution is necessary to provide for the blank required to produce the end-point with the indicator. When this standard potassium iodide solution is used in the titration of excess silver nitrate in blood chloride determinations, the same blank of 0.03 cc. is subtracted from the titration value obtained.
4. Palladious nitrate indicator solution.

Palladious nitrate	0.13 gram
Nitric acid, conc	16 cc.
Water to make	100 cc.

This solution keeps indefinitely.

Technique of method

To 2 cc. of plasma or whole blood in a 25 cc. volumetric flask, add about 6 cc. of water, and then 15 cc. of 2 per cent sulphosali-

cylic acid. Dilute to volume, shake, allow to stand five to ten minutes, and filter. To 10 cc. of the water-clear filtrate in a 25 cc. volumetric flask, add 5 cc. of standard silver nitrate solution, and dilute to volume. Add a small pinch of kaolin to aid the coagulation of the silver chloride formed, shake thoroughly, allow to stand five to ten minutes, and filter. If the first few drops of the filtrate are cloudy, pour back through the filter to obtain a clear solution. To 10 cc. of the filtrate in a small Erlenmeyer flask, add 0.2 cc. of palladious nitrate indicator and, using a micro-burette, titrate with standard potassium iodide to the first brown color. The end-point is very distinct and permanent.

Calculation of results

The amount of sodium chloride present may be calculated from the following formula:

$$\left.\begin{array}{c}\text{Milligram of}\\ \text{NaCl per 100}\\ \text{cc. of blood}\\ \text{(or plasma)}\end{array}\right\} = \left\{2 - \frac{\text{KI used} - \text{titration blank}}{2}\right\} \times \left\{\begin{array}{c}\text{mgm. of}\\ \text{NaCl per}\\ \text{cc. of}\\ AgNO_3\end{array}\right\} \times \left\{\begin{array}{c}\dfrac{100}{\text{Blood (or plasma)}},\\ \text{equivalent of}\\ \text{filtrate used}\end{array}\right.$$

$$= \frac{4 - (\text{KI used} - 0.03)}{2} \times 1.28 \times \frac{100}{0.32},$$

$$= 4 - (\text{KI used} - 0.03) \times 200.$$

Thus, to find the number of milligrams of sodium chloride in 100 cc. of plasma (or whole blood), subtract 0.03 (the titration blank) from the number of cubic centimeters of KI used, then subtract this figure from 4, and multiply the difference obtained by 200.

Accuracy of method

Proof of the accuracy of the proposed method and of the sensitivity of palladious nitrate as an indicator is given by the results obtained when varying amounts of hydrochloric acid of known normality were used in place of blood filtrate and their chloride contents were determined according to the latter part of the method as outlined. Table 1 shows that the amount of chloride found in each case corresponds closely to that actually present.

TABLE 1

COMPARISON OF THE THEORETICAL CHLORIDE CONTENTS OF VARYING AMOUNTS OF STANDARDIZED HYDROCHLORIC ACID SOLUTIONS WITH THOSE FOUND BY THE PALLADIOUS NITRATE METHOD

HYDROCHLORIC ACID (1 cc. = 0.559 mgm. NaCl)	CHLORIDE AS NaCl	
	Theoretical	Found*
cc.	*mgm.*	*mgm.*
9.0	5.03	4.99
9.1	5.09	5.07
9.2	5.14	5.12
9.3	5.20	5.19
9.4	5.26	5.22
9.5	5.31	5.27
9.6	5.37	5.36
9.7	5.42	5.43
9.8	5.48	5.46
9.9	5.54	5.50
10.0	5.59	5.57

* Average of duplicate determinations.

TABLE 2

COMPARISON OF PLASMA CHLORIDE VALUES OBTAINED BY THE MCLEAN-VAN SLYKE METHOD AND THE PALLADIOUS NITRATE METHOD

SAMPLE NUMBER	NaCl PER 100 CC. BLOOD PLASMA*	
	McLean-Van Slyke method	Palladious nitrate
	mgm.	*mgm.*
1	640	644
2	596	590
3	556	559
4	596	590
5	611	608
6	554	548
7	596	588
8	550	547
9	541	550
10	635	634
11	571	578
12	604	597
13	589	586
14	587	580

* Results with both methods are averages of duplicate determinations.

Table 2 demonstrates even more convincingly that the method is accurate for the determination of the chlorides of blood, as it shows, by typical examples, the close agreement between the plasma chloride figures obtained by the proposed method and those secured with the procedure of McLean and Van Slyke.[1] Inasmuch as these investigators obtained, by their method, values which agreed within 0.51 per cent with those found by fusion, we may assume that our method gives an accurate estimate of the true chloride content of plasma.

Finally, attention should be called to the fact that, according to our experience, the chloride content of whole blood may be determined by this method with the same degree of accuracy as has been demonstrated for plasma.

CONCLUSION

Our desire to secure a simple indicator, which would give a sharper and more permanent titration end-point than it is possible to obtain with sulphocyanate and ferric alum, has been more than satisfied by the introduction into blood chemistry of palladious nitrate for the titration of silver nitrate with potassium iodide. This indicator requires no specific buffering and gives a sharp, clear, easily recognizable end-point lasting at least over night.

SUMMARY

1. A method has been proposed for the determination of the chlorides of whole blood or plasma.

2. By introducing sulphosalicylic acid as the protein precipitating agent and palladious nitrate as the indicator in titrating excess silver nitrate with potassium iodide, a rapid, accurate procedure has been developed.

3. The end-point is sharp, clear, permanent and easily recognizable.

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THE PRESENT STATUS OF CLINICAL LABORATORY MEASUREMENTS WITH A NOTE ON THE PHOTO-ELECTRIC EFFECT*

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GENERAL CONSIDERATIONS

Excepting only the descriptive, it is generally recognized that every branch of science is fundamentally quantitative and that improvements in measurements are necessary for scientific progress. Thus the problems of the pure sciences are often wholly matters of measurement while those of the applied sciences are inextricably bound up with the very concrete matter of efficiency of production. Workers in the pure and applied sciences are, therefore, always keenly aware of the importance of improving methods of measurement.

That physicians do not so clearly comprehend the nature and importance of measurements is evident in many ways. Thus a recent issue of a first rate medical journal contained, among others, two papers, one of which gave data to show that protein fractionations could be made more precisely by interferometry than by refractometry, while the other gave clinical data of cases in which proteinuria was a prominent characteristic, designating the protein concentrations by one or more crosses. Evidently a forward looking editor saw nothing incongruous in presenting at the same time methods for estimating the same material which in one instance are of extreme refinement and in the other of extreme crudity. Such instances are not at all unusual; on the contrary, practically every text on clinical pathology has numerous ex-

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amples of indiscrimination between qualitative, semi-qualitative and quantitative methods.

Perhaps the dual conception of the practice of medicine as being partly art and partly science accounts for the inchoate appreciation of the nature and value of precise measurements, because duality naturally tends to confuse and the confusion seems to make it difficult for many physicians to distinguish clearly between what is art and what is science in medicine. However that may be, it is, nevertheless, certain that the art of diagnosis only begins and can only function to best advantage after science has developed as accurate and complete information as possible about a case. Physicians who are satisfied with anything less than the best information that science can give them about their cases, therefore, fail to do justice to themselves, their patients and their art.

Of the tests most commonly applied in practice to develop clinical information, those for protein, sugar and the formed elements in urine are good examples of the illusory habit of trying to draw quantitative deductions from purely qualitative tests, which still persists among physicians who have not yet learned that the newer quanitative methods, at no more cost in time and trouble, supply much more useful information than the older hit-or-miss qualitative methods.

Furthermore, those clinicians who follow the trend of modern experimental medicine already insist on knowing not its mere concentration but the rate at which patients excrete substances of particular interest, because such information not only has much more definition and clinical value but is unquestionably the truest criterion for comparing samples excreted at different times by the same individual. Being a simple correlation of time, volume and concentration, the rate of excretion, of course, depends upon accurate quantitations of the excreted substances, and the responsibility of providing better quantitative information rests squarely upon clinical pathologists.

All good physicians aim at earlier and earlier diagnosis, but advancement in this extremely important field is hindered by the insufficient sensitivity of many of the tests in common use. Of

these the tests for indican and ketones in urine may be taken as examples, and here again clinical pathology has the obligation to provide not only more accurate but also more definite earlier information.

Again, there are certain kinds of very valuable information which are not available in practice as early and as generally as they should be because their technics are somewhat complicated and time-consuming. Blood cholesterol, calcium, non-protein nitrogen and urinary ammonia are examples of this kind of information, and for the good of the public it is, of course, desirable that such technics be brought within the realm of clinical routine.

If there is any branch of medicine which is essentially scientific and therefore quantitative, it is that which has come to be known as clinical pathology, and it is the function of the clinical pathologist not only to provide complete and exact laboratory information but also to interpret such information and advise the kinds of information which may or may not be useful or suggestive in a particular case. Clinical pathologists should, therefore, be familiar with the newly won facts of experimental medicine because that special knowledge, hand in hand with the ability to perform more complicated procedures like sulfur partition or protein fractionation, may often lead to clearing up obscurities which surround doubtful cases.

There are other considerations which also show how vital to the practice of medicine is the advancement of clinical pathology along lines which broaden its scope and refine its technics so as to make them more precise and practical and therefore more generally useful. Inevitably every improvement in the accuracy and sensitivity of clinical pathological technics registers an increase in clinical abilities. Thus the progress of medical science depends upon improving methods of measurement.

Measurement of the many materials of clinical interest in the various body fluids usually involves both chemistry and physics. The chemistry has, of course, been contributed by painstaking pioneer work of the chemists who, unfortunately, have not been accustomed to restricting bench manipulations to a minimum or to dealing with limited amounts of material. Thus the litera-

ture of biochemical technics is rich in excellent methods which have never passed beyond the status of mere records and remain clinically useless because too complicated and time consuming. In fact, it has been the history of many of our most valuable clinical methods that after publication the technics undergo a series of modifications and simplifications extending often over years before they become generally useful for clinical routine. Undoubtedly the demands of science for precision and the demands of economics for simplicity and rapidity are somewhat conflicting, but the many successful reconciliations which have already been accomplished point unmistakably to the way of improving the practice of medicine.

Outside the laboratory when information is immediately needed, as for instance in the operating room or at the bedside, a reasonable compromise between speed and accuracy is expedient, but conceding accuracy to convenience in the laboratory is never justifiable unless the resulting effects have been rigorously considered and are clearly understood because every loss in accuracy is a loss in scientific ability. That this situation is clearly understood by many clinical pathologists is evident from the continual search for better and more precise methods. That others do not appreciate it is evident from their willingness to employ inferior methods, usually because they have not progressed beyond a qualitative state.

HEMOGLOBINOMETRY

Its general application and great clinical importance account for the fact that hemoglobinometry is performed oftener than any other blood test. It also happens that during the past few years in journals and meetings both clinical pathologists and clinicians have expressed marked dissatisfaction with current hemoglobin methods. Hemoglobinometry, therefore, appropriately illustrates the present status of colorimetry in clinical laboratories.

Van Slyke's oxygen capacity and iron determinations are admittedly the best of all hemoglobin methods. While exceedingly valuable for standardizing purposes and for checking other methods, they are, unfortunately, too exacting for clinical work.

Of the methods practically applied, some crudely measure the colors of a stain or smear of native blood. The other methods by more or less quick and simple manipulation convert hemoglobin into oxy-hemoglobin or the more stable acid hematin. All of them compare the color of the sample with some kind of standard by means of some optical device.

Not one of the methods has won its way into general use, and all of them have been criticized either as to accuracy or practicability. The existing situation may, therefore, be described as one in which many different methods giving inaccurate and different kinds of results are now being used in our clinical laboratories.

If some kind of animal or other source of supply of a stable hemoglobin solution containing say 15 grams per 100 cc. were conjured up, all of the perplexities and difficulties that now beset hemoglobinometry would quickly disappear because such a mythical standard would enable a clinical pathologist to determine hemoglobin with whatever precision he desired. Thus, one could settle on a weak looking standard and dilute the sample until the colors looked alike, or one might make different dilutions of the imaginary standard so as to have a series of concentrations in test tubes to slap against and compare with the sample in some sort of perforated box.

On the other hand, a clinical pathologist intent on developing the kind of information which can be relied upon for close diagnostic reasoning, to tell if a patient is anemic or not in borderline cases, to detect and help follow the course of hemorrhage, to enable him to appraise the effects of treatment, or to furnish data for correct statistics, could secure the necessary precision by using an accurate photometer like a well made Duboscq colorimeter. On final analysis, then, it is clear that the absence of standardizing difficulties resolves the matter of precision into a mere choice of measuring device.

Unfortunately, our imaginary standard is only one of many ideal standards for measuring biologic materials which are also lacking. In the case of hemoglobin, some supply the deficiency by meticulously preparing standards from chance specimens of

blood subjected to careful oxygen capacity or iron determination. Although theoretically and practically correct, the preparation and maintenance of such standards are impossible in many clinical laboratories. It therefore happens that much ingenuity has been expended in attempts to secure satisfactory substitutes. These usually take the form of colored liquids or glasses.

The liquid standards are more or less stable solutions of inorganic materials or dyes. Their great deficiency, however, is that which they have in common with the colored glasses, and this defect is well illustrated by Newcomer's[2] experience.

As a result of his painstaking search for a standard suitable for use in place of a certain definitely prepared concentration of acid hematin, Newcomer found a substitute in the form of a disc cut from a particular melt of glass which happened to have a spectral transmission similar to that of his acid hematin. The Duboscq colorimeter was adapted for the disc and the manufacturer supplied standards cut from the original batch of glass as long as it lasted. The original Newcomer method is now necessarily limited to those fortunate enough to have one of the standard discs because the most expert technologists have never been able to reproduce the glass. This is all the more regrettable because none of the currently used glass hemoglobin standards have the same spectral transmissions as the samples and Newcomer's is the only hemoglobin method employing a glass standard which is based upon correct scientific principles.

In the early days of clinical colorimetry when the underlying optics were not so well understood by chemists and clinical pathologists many attempts to avoid the standardizing troubles of Duboscq colorimetry were made by employing solutions of dyes or inorganic materials. Experience, however, soon taught that Duboscq colorimetry is inaccurate when the spectral transmissions of standard and sample are not the same. Such colored liquids, like the colored glasses, are therefore unfit for critical comparisons with the samples they are supposed to measure, and the present unsatisfactory state of hemoglobinometry and other quantitations by colorimetry must be laid to the extensive use of standards which only roughly resemble and cannot be critically compared with the unknown sample.

JUNIOR SCOPOMETRY

Owing to the nature of dispersed materials the standardizing troubles of nephelometry and comparison turbidimetry are even greater than those of colorimetry and they account for the failure of these highly sensitive and potentially very valuable methods to give better results than the ancient disappearance or extinction criterion which needs no standards at all. To exploit this feature to the utmost advantage, the disappearance criterion was refined and improved and as made available in the Junior Scopometer[1] measures turbidity with greater accuracy than other clinical methods and with even less time or trouble than the crudest of existing devices.

As a result of efforts to obtain similar advantages in colorimetry a novel extinction method of colorimetry was later incorporated in the Junior Scopometer which frees hemoglobinometry and other colorimetric methods of standardizing difficulties by substituting for the usual standards reference graphs or tables showing the equivalents of concentrations and scale readings.

In the case of hemoglobin, for instance, such a calibration is made by determining the hemoglobin content of a sample of blood known to be higher than normal by the exacting oxygen capacity or iron method. Other parts of the same sample, diluted so as to have a series of concentrations covering the desired range, are subjected to some pre-determined acid hematin or oxy-hemoglobin method and the disappearance points then measured in the Junior Scopometer. By plotting the known concentrations against the Scopometer scale readings a calibration is obtained which thereafter need never be made again because the scale readings obtained by similarly treating subsequent samples are always referable to the original calibration.

While the Junior Scopometer is more generally applicable and gives more uniform and accurate results than the so-called permanent standard methods (i.e., colored glasses or liquids in tubes) there are certain disadvantages inherent in the physiological optics of its extinction criterion which depend upon the fact that the human eye cannot mark the disappearance of an object as critically as it can compare the brightness (color) of two specimens

with the aid of such refined optical means as a good photometer of the Duboscq type.

NOTES ON THE PHOTO-ELECTRIC EFFECT

The variabilities and limitations of human vision are such that physicists have always dreamed of emancipating optical measurements from the bias of personal equation, and a promise of the dream coming true was made almost half a century ago by the discovery of the photo-electric effect which transforms light into electricity by means of photo-electric cells. These take the form of glass bulbs containing two electrodes; one, the cathode, is light sensitive and emits electrons when exposed to light; the other, or anode, when subjected to positive voltage attracts and gives direction to the electrons leaving the cathode. An efficient photo-electric cell is, therefore, a valve emitting an electric current which is linearly proportional to the stimulus of incident light.

That the earliest experimenters applied such a device to photometry is not surprising, and, as a matter of fact, photo-electric photometers were constructed and used by physicists within a year or two after Hertz's discovery. The early instruments measured the minute currents emanating from the cells with the most sensitive of known devices such as electroscopes and electrometers, and this, with other practical difficulties, necessarily restricted their operation to experimental physicists. Following the early experimental work it is interesting to note that while the theoretical literature of photo-electricity was constantly growing practical attempts to apply photo-electricity to photometry remained at a standstill until the invention of the thermionic amplifying tube by De Forest.

As it conferred other abilities as well as enabling measurements of the minute photo-electric currents, amplification naturally stimulated a renewed and enthusiastic interest in the practical possibilities of photo-electricity which have since been realized and brought to the public notice in the form of talking movies, counting, sorting, smoke recording and advertising devices, television, etc.

Amplification also made photo-electric star, lamp and spectro-

photometry practicable and has since been applied in many devices designed to improve other photometric procedures such as colorimetry and turbidimetry. Of these it appears that many have never been carried beyond the stage of design, that some were built for frankly experimental purposes, and that others, like Sheard and Sanford's[3] photo-electrometer, are satisfactory in the hands of their designers.

The photo-electric effect, or electric eye, as it has been aptly called, being far superior to human vision in its ability to mark the degree of brightness without a comparison standard, offers the possibility of combining in one method all of the advantages and conveniences of Junior Scopometry with as good or better accuracy than that of the best visual photometry. That such an instrument would be ideal for clinical laboratories is, of course, self-evident, and the fact that none is even now generally available must be laid to difficulties connected with the practical application of photo-electricity.

This becomes immediately apparent to any one who experiments with existing or proposed devices because all of the available amplifying arrangements require at least five different unvarying intensities of electricity (light, plate voltage, thermionic tube elements). These are usually supplied by different kinds of batteries which necessitate both permanent and temporary connections in addition to the variable resistances, potentiometers, and other meters and accessories needed for adjustments that are necessary to maintain calibration. Besides these there are other variables which make amplification devices hopelessly impracticable for any but the exceptional clinical laboratory because the conditions under which measurements are made in clinical laboratories demand instruments having the utmost simplicity of design, rigidity of construction, the fewest possible adjustments, and the highest degree of stability with the greatest possible convenience of operation.

In attempts to apply the electric eye to Scopometry I tested out the possibilities of various glow tubes and other amplifying devices with different circuits, and in the course of these experiments was able to secure a number of different ar-

rangements which functioned successfully when continuously watched, adjusted and checked with meticulous care. In fact, under such conditions an astounding degree of sensitivity was obtained with several setups. Because of the intricacies and complications, however, which seem to be inseparable from present methods of amplification none of them, by any stretch of one's imagination, could be considered practicable and safe enough to put into the hands of the usual run of laboratory technicians.

Believing it essential that an instrument intended for clinical laboratory measurements must be as nearly fool proof as possible, I then explored other approaches to the problem which were free from the need of amplification and supersensitive electrical measuring devices. As a result of these experiments I finally secured a setup which has proved so satisfactory that it is still in routine use in the Prudential Laboratory. From figure 1 it will be seen that a beam of light taken from an incandescent lamp is split into two by means of a partly transparent and partly mirrored glass. One of these optical paths goes straight through transparent stripes of glass to a photo-electric cell, while the other is reflected by mirrored stripes to a similar photo-electric cell. The cells are connected with a rugged short period galvanometer in a simple Wheatstone bridge circuit so that the currents from the photo-electric cells balance one another when they are equal. For balancing the light traversing the two optical paths there is a provision in one for interposing the specimen to be measured and in the other for a diaphragm whose aperture can be increased or diminished at will. Thus a specimen placed in one path is measured by simply turning a pinion which changes the aperture of the diaphragm in the other path until the galvanometer registers a perfect balance by pointing to zero. At this point a reading of the scale attached to the diaphragm gives the measure of the specimen when referred to a predetermined calibration like those of the Junior Scopometer.

Such a calibration for hemoglobin (acid hematin) is seen in figure 2 which also indicates the unusual sensitivity of the method without the light filters used in Junior Scopometer colorimetry.

Figure 3 shows the calibration of a graduated series of sodium picramate solutions whose run of brownish red colors are similar to those of the di-nitro salicyclic and picric acid sugar reduction methods.

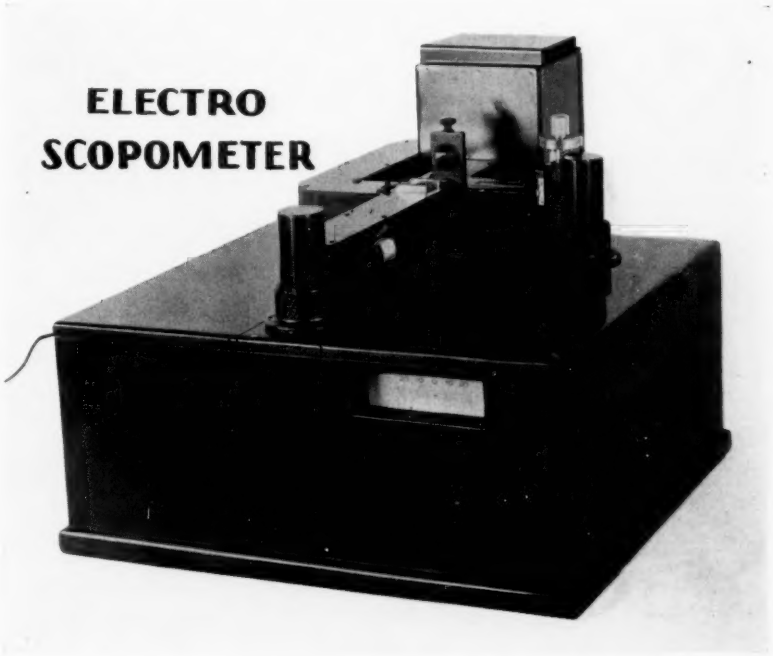

FIG. 1. EXPERIMENTAL PHOTO-ELECTRIC SETUP WITH PROVISIONS FOR MEASURING SPECIMENS BY EITHER REFLECTED (LEFT) OR TRANSMITTED LIGHT (CENTER)

Adjustable diaphragm with scale on right. Note the single electrical connection for house current. In its finished form this device will be known as the Electro Scopometer.

Figure 4 gives a calibration for measuring blue solutions like those obtained with the sugar, phenol, uric acid and other molybdic reduction methods of Folin and Benedict.

Figure 5 indicates the extraordinary sensitivity with which the method measures turbidities by transmitted light as shown by the calibration for counting red blood cells.

Figure 6 shows the results of two experiments made on the same material. One of them, to determine the stability of a particular suspension, was made by precipitating a graduated series of serum

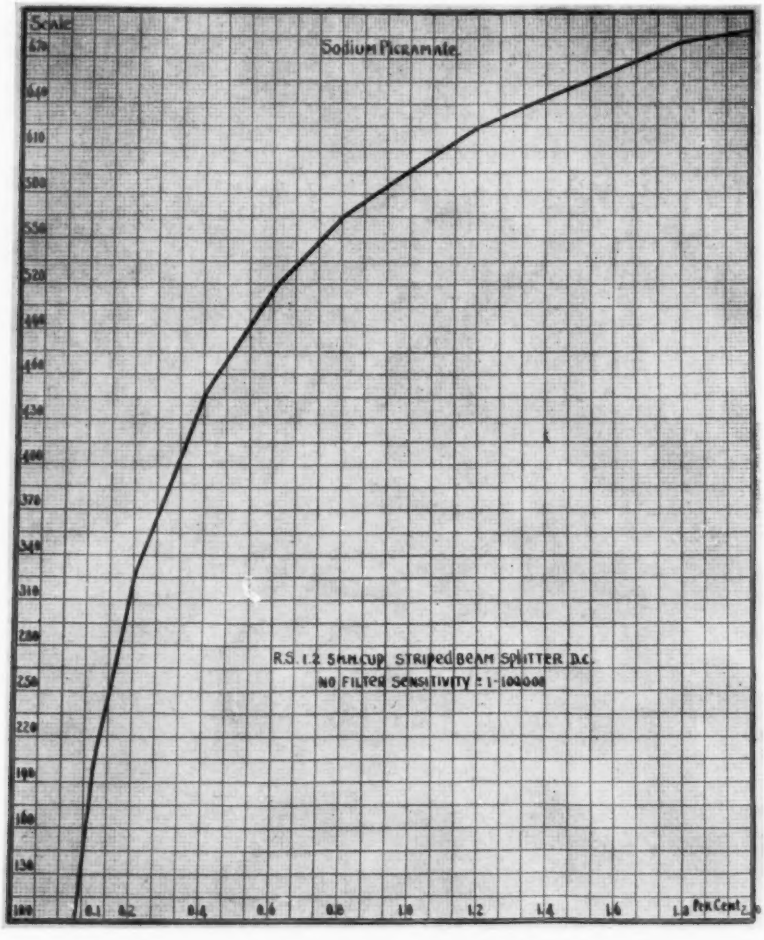

FIG. 3

protein concentrations with Exton's reagent and plotting the concentrations against the scale readings obtained with the instrument and then re-reading the suspensions after twenty-four hours standing. The results of this experiment indicate remarkable

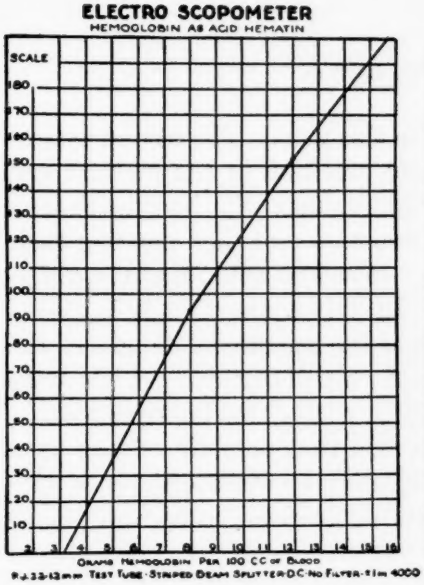

FIG. 2

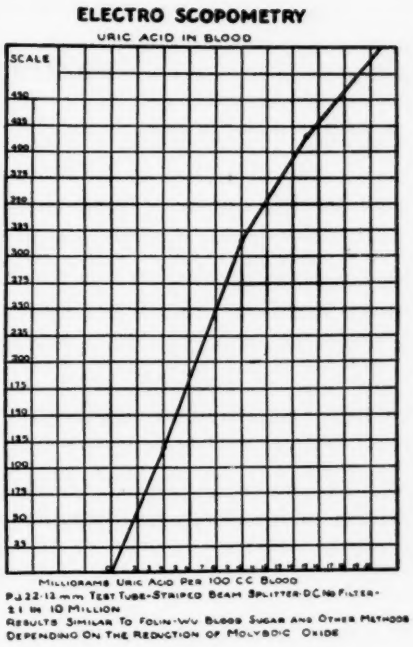

FIG. 4

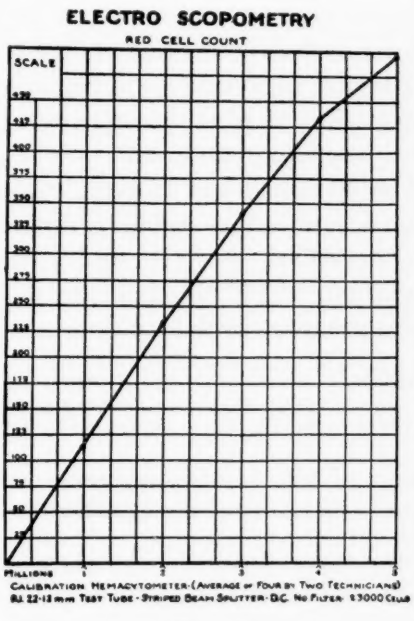

FIG. 5

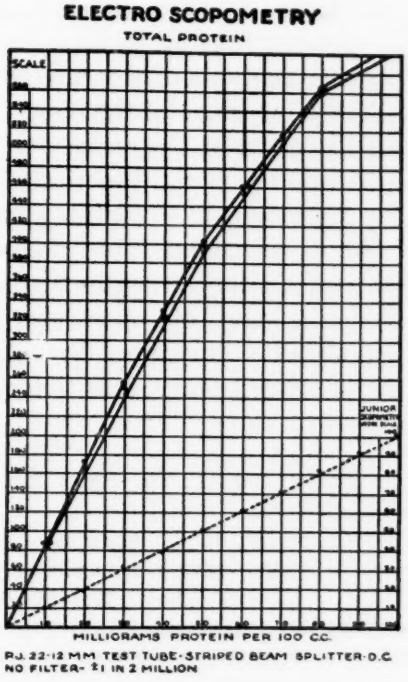

FIG. 6. Stability experiment indicated by lines. Precision experiment indicated by circles.

stability of suspensions obtained in this way. The second experiment was designed to indicate the precision of the method and was carried out by giving three individuals who had never seen the instrument a few minutes instruction and then plotting their single readings also on the graph. It will be noted that the differences are less than 1 per cent. In this connection it is also of interest to note that the precision of the instrument taught us the necessity of refining some bench manipulations which were hitherto regarded as satisfactory (i.e., with visual instruments).

In conclusion it remains to be said that only those who have enjoyed the opportunity can adequately appreciate the ease with which accurate measurements are made possible by the photo-electric effect.

SUMMARY

The present status of clinical pathology is discussed with special reference to improving its usefulness by more informative and precise methods than are now generally employed, taking hemoglobinometry as an illustration of the fundamental need for improving methods of measurements.

The advantages of the photo-electric effect over visual methods are discussed and experiments in trying to overcome difficulties connected with the practical application of photo-electricity to the requirements of routine clinical pathology are cited.

An experimental photo-electric setup which has proven decidedly satisfactory in routine work on account of its stability, rapidity and ease of operation is described and its universal applicability illustrated by calibrations which also indicate the extraordinary range, sensitivity and accuracy of the method.

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EXPERIMENTAL FAT NECROSIS IN VARIOUS VERTEBRATES*

M. PINSON NEAL AND MAX M. ELLIS

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Langerhans[2] injected an extract prepared from the pancreas of rabbits into nine rabbits and three dogs, and obtained in one of the rabbits the first experimental fat necrosis. Except for the small degree of success, numerically speaking, and for the small number of animals used in the experiment, in view of the fact that negative results were obtained in the dogs, a conclusion might have been drawn that the extract was not potent, or functional in the sense of its ability to produce fat necrosis in heterogeneous species.

Jung,[1] by placing pieces of dog's pancreas in the abdominal cavity of rabbits, and Wells,[5] by injecting cats, dogs and rabbits with an extract prepared from fresh pancreas of the hog, produced fat necrosis. The results of these two investigators proved that the fat necrosis producing substance was not, therefore, one limited to homogeneous species.

The work here recorded was taken up with the intent to add further proof to the recorded facts as to the non-homogeneous specificity of the fat necrosis producing substance, and also to determine the response in different types of vertebrates to the action of this particular ferment or enzyme on their fat deposits. This diversity of species brings in the questions of species specificity, of variation in the response of the fat deposits in different species, of the hydrogen ion values for the different vertebrates, and of the body temperature as possible factors influencing the experimental production of fat necrosis.

* Read before the Ninth Annual Convention of the American Society of Clinical Pathologists, Detroit, Michigan, June 20–23, 1930.

EXPERIMENTAL PROCEDURES

The vertebrates used fall into two main groups,—the cold-blooded and the warm-blooded varieties. In the cold-blooded group, there have been used: *Lepisosteus platystomus*, the short-nosed gar, *Cyprinus carpio*, the German carp, and *Macroclamys pseudo-geographica*, and *Chrysmes belli cinerea*, two types of turtles. The cold-blooded animals were kept in aquaria with a rather constant temperature of 18° to 20°C. Two groups of warm-blooded vertebrates were used. One, the mammalian group, included *Mus decumanus*, the white rat, and *Canis familiaris*, the common dog, having a normal temperature of around 37°C. In the other, the avian group, there were used *Gallina domestica*, the domestic hen, and *Columba livia*, the street pigeon, for which the respective normal body temperatures are given[4] as 40.5° to 42°C., and 41° to 43°C.

TABLE 1

SUMMARY OF POSITIVE RESULTS OBTAINED BY SUBSTANCES EMPLOYED IN THE EXPERIMENTAL PRODUCTION OF FAT NECROSIS

SPECIES OR TYPE ANIMAL	SUBSTANCE INJECTED							
				Lipase fractions derived from:				
	Commercial pancreatin	Fresh hog's pancreas	Dog's pancreatic secretion	Commercial pancreatin	Hog's pancreas	Peanuts	Sunflower seed	Castor bean
Fish	+	0	0	0	0	0	0	0
Turtles	+	0	+	0	0	+	0	0
Hens	+	0	0	0	0	+	0	0
Pigeons	+	0	0	0	0	0	0	0
Rats	+	+	+	+	+	+	+	+
Dogs	+	0	0	0	0	0	0	0

+ = positive; 0 = no test.

The investigations are based entirely on intraperitoneal injections into fish, turtles, hens, pigeons, rats and dogs, of various substances containing the fat necrosis producing enzyme, lipase.[3] The primary aim has been to determine the ability of the various extractives to produce fat necrosis in this varied group of verte-

brates. These records include only those animals that survived injections long enough or had doses sufficiently large to develop lesions of fat necrosis.

Injections into fish

Injections of pancreatin (Armour's lot No. 205316) into German carp and gar resulted in the production in twenty-five hours of fat necrosis in one carp out of four that were injected, and in one gar (fig. 1) out of six. This low percentage of positive results was to a certain degree dependent upon the fact that soon after

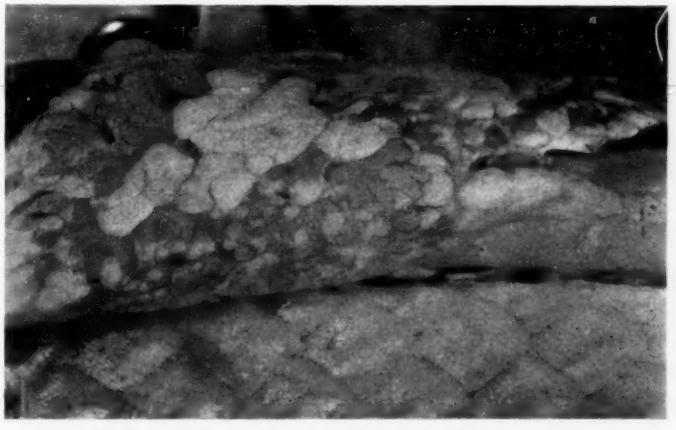

FIG. 1. GROSS LESIONS OF FAT NECROSIS TWENTY-FIVE HOURS AFTER INJECTION OF ARMOUR'S PANCREATIN. GAR NO. 6

being received and injected, most of the fish died, probably as a result of trauma received in shipping.

Injections into turtles

Emulsion of pancreatin (Armour's lot No. 205316) was injected into seven turtles, and of these, four developed fat necrosis, as demonstrated at forty-seven and ninety-six hours, and six days. Three turtles yielded negative findings at from seventy to one hundred and twenty hours.

Pancreatic secretion obtained from three dogs through canula

placed into the pancreatic duct, pooled, and then injected into four turtles, yielded two positive results at the periods of sixty-five and one hundred and twenty hours (figs. 2 and 3). Two turtles receiving like doses of dog's pancreatic secretion gave negative findings at fifteen hours and sixteen days.

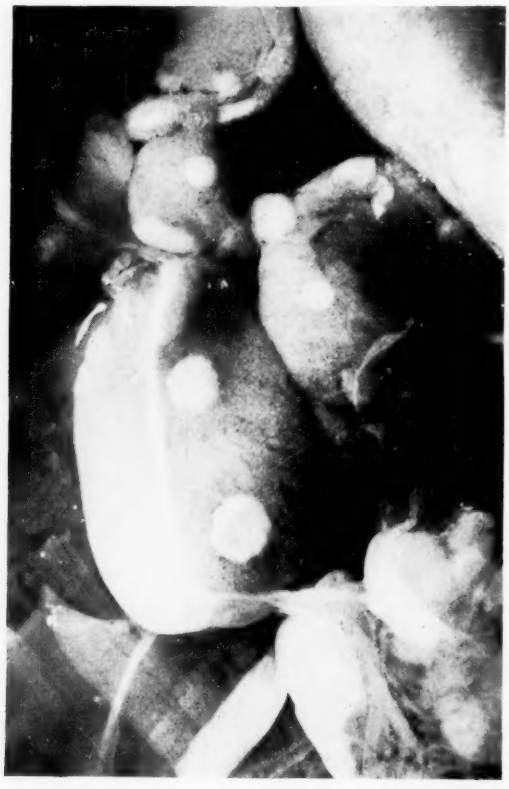

FIG. 2. GROSS LESIONS OF FAT NECROSIS SIXTY-FIVE HOURS AFTER INJECTION OF PANCREATIC SECRETION FROM DOG, (ENLARGED ×11). TURTLE NO. 13

The lipase fraction, "arachis concentrate" derived from peanuts and injected into five turtles, resulted in fat necrosis in two of them at ninety-six hours. Three others showed no fat necrosis in its usual sense, but did reveal marked changes in the contained eggs at seventy-two and ninety-six hour observations.

All turtles were killed at the stated time periods. There were no fatalities, hence no possibility for post-mortem degenerative changes to play a rôle in the recorded observations.

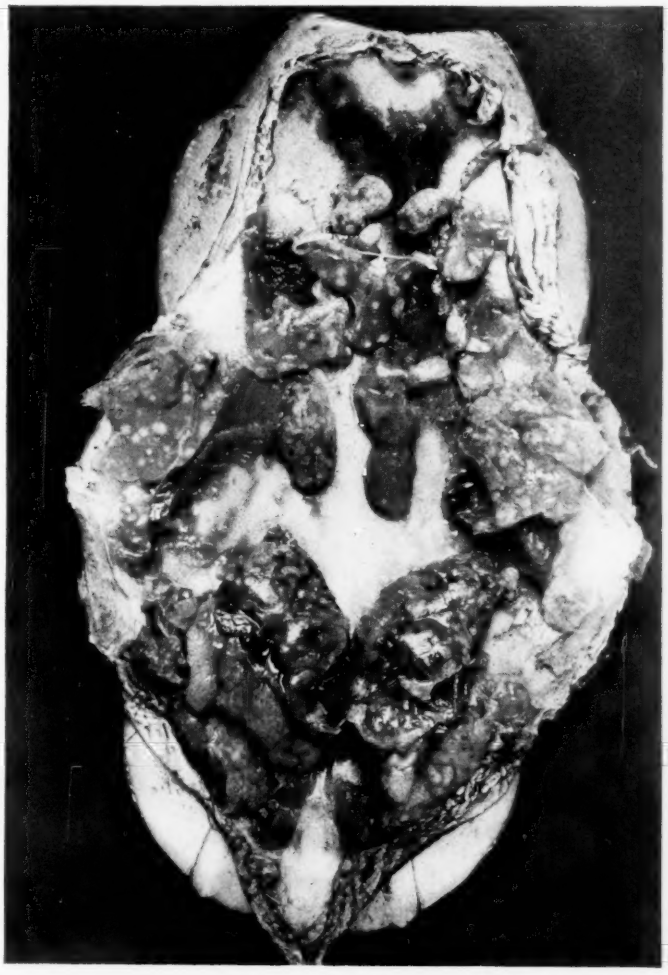

FIG. 3. GROSS LESIONS OF FAT NECROSIS 120 HOURS AFTER INJECTION OF PANCREATIC SECRETION FROM DOG. TURTLE NO. 14

Injections into hens

Emulsion of pancreatin (Armour's lot No. 205316) injected into three adult hens, yielded a positive result when the hen was

killed at the end of the seventy-hour period. A second hen died from hemorrhage within two hours, and the third was dead and partially decomposed at nineteen hours.

Arachis concentrate injected into three hens produced at twenty and forty-six hours, positive results in two, but at the end of seventy hours, no lesion was found in one animal.

Injections into pigeons

Emulsion of pancreatin (Armour's lot No. 205257) was used in the injection of eleven pigeons. Of this number, six gave positive results for fat necrosis at periods of from five hours to eight days. Five pigeons received similar doses of pancreatin emulsion but failed to show fat necrosis at periods of time ranging from four to seventy-five hours.

Injections into rats

Emulsions of pancreatin (Armour's lots Nos. 205257 and 205316) were injected into forty-nine white rats. Of this group, forty developed lesions of fat necrosis as demonstrated at from three hours (histologic findings only at this time) after injections up to and including thirteen days. Two rats gave negative findings on the seventeenth day after injection, as did three on the twenty-first day. The absence of findings after the thirteenth day indicated healing had taken place, for the lesions found in two rats at that time were histologically almost healed processes.

Two rats were given a solution prepared from macerated fresh pancreas of the hog, and showed fat necrosis at sixteen and one-half hours. Injections into ten rats of the lipase fraction from hog's pancreas produced positive results in six (fig. 4) at from twenty-one to ninety hours. Four rats that also received preparations of extract of hog's pancreas gave negative findings at from six to seventy-two hours.

Five rats were given pancreatic secretion pooled from three canulized dogs. Of these, three showed fat necrosis at from fifteen to ninety-six hours, whereas two showed no such lesions at fifteen hours.

Extracts from sunflower seed (*Helianthus annuus*) refined down to the fraction now recognized as lipase carrying, when injected into three rats gave in one at seventy-two hours, many foci of macroscopic and microscopic fat necrosis. The other two which died between six and twenty-one hours, were negative for these lesions.

Two different preparations from peanuts (*Arachis hypogaea*) were used in injections of white rats. One was termed "arachis

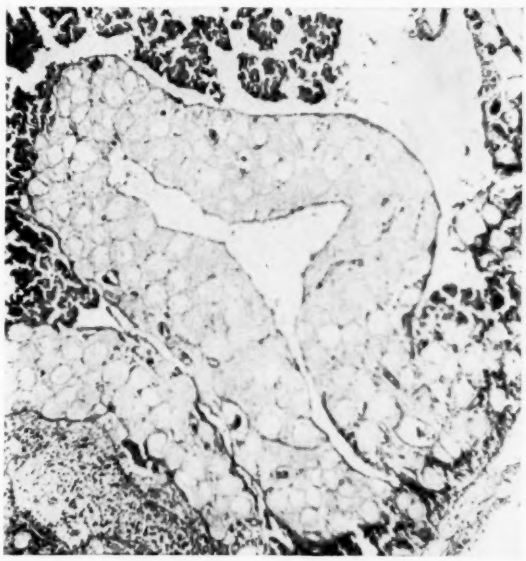

FIG. 4. HISTOLOGIC PREPARATION OF FAT NECROSIS SEVENTY-TWO HOURS AFTER INJECTION OF LIPASE FRACTION, ACID SERIES, FROM HOG'S PANCREAS (ENLARGED ×80). RAT NO. 56

alba," and the second "arachis concentrate," a brown mixture representing a more highly refined and concentrated extract of the lipase. Injections into twenty-seven rats of these products obtained from peanuts, gave fat necrosis in seventeen. Of the fifteen receiving arachis alba, seven showed fat necrosis at from seventy-one hours to eight days. Observations on eight showing no fat necrosis were made at periods of from twenty hours to five days. Ten of the twelve rats receiving arachis concentrate

developed fat necrosis at intervals of from six hours to five days. The other two rats gave negative findings at seventy hours and five days.

Injections into dogs

Two dogs (fig. 5) each injected with emulsion of pancreatin (Armour's lot No. 205316) and killed ninety-three hours later, showed marked fat necrosis in all intra-abdominal fat deposits.

These results are summarized in the tabulation.

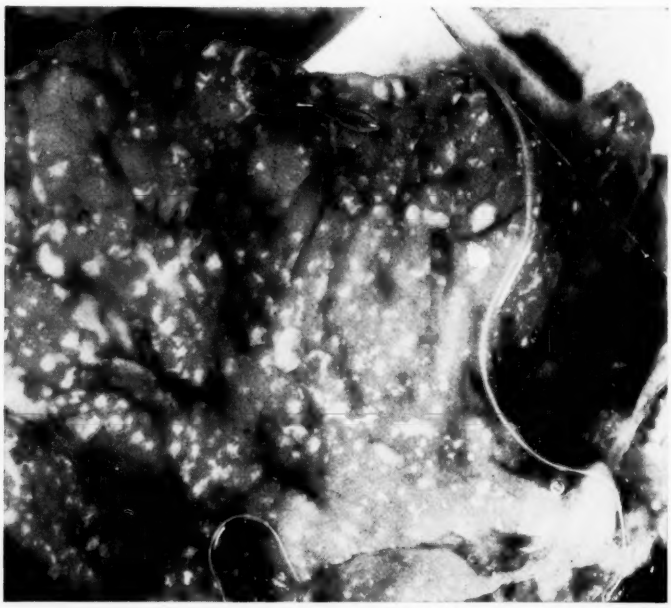

FIG. 5. GROSS LESIONS OF FAT NECROSIS IN OMENTUM NINETY-THREE HOURS AFTER INJECTION OF ARMOUR'S PANCREATIN. DOG NO. 2

FACTORS OF SPECIES DIFFERENCES

Species specificity

Certain of the vertebrates, even species of vertebrates, are immune or highly resistant to some of the common diseases to which man or other vertebrates are subject. Some of these species resistances can be accounted for by the factor of normal

or variable body temperatures, for example, Pasteur's well-known experience with anthrax in fowls where body temperatures were lowered. Some of the individual and species immunity, or lack of susceptibility as it appears to be in some cases, cannot with our present knowledge be measured or determined except by direct exposure to the factor or factors that are known commonly to produce the series of developments or lesions in others. Insofar as fish (carp and gar), turtles, chickens, pigeons, white rats, and dogs are concerned, there is no such species resistance against the specific action of lipase in its production of fat necrosis.

Differences in the fat of cold-blooded and warm-blooded vertebrates

In the warm-blooded species, as a part of the body metabolism, fat is stored in various locations; these storage centers or supplies are drawn upon for heating the body, and also act as contributors in the maintenance of general body energy. In the cold-blooded types, the fat deposits or depots are somewhat different from those of the warm-blooded species, and are subsidiary to the reproductive activities of the individual. In the pre-reproductive stage of the cold-blooded vertebrates, fat deposits are most in evidence. As the reproductive stages mature, the fat deposits decrease in amount, and often disappear.

In the turtle, some of the fat bodies are of a very primitive, embryonic type. Grossly they appear as a lymphoid-adipose tissue.

It was found that fat necrosis could be produced equally well in two species of cold-blooded vertebrates, fish and turtles, as well as in warm-blooded types, hens, pigeons, rats, and dogs. The type of fat, that is, whether purely energy and heat-producing stored deposits, or that type stored for the part it plays in the reproductive cycle and activity, does not interfere with the ability of lipase to produce fat necrosis in these particular fat bodies.

Hydrogen ion concentration values of the vertebrate fluids as a factor in the production of fat necrosis

The pH values of normal blood serum for the vertebrates in which fat necrosis was produced were: rat, 7.3; dog, 7.3 to 7.5; turtles, 7.5; pigeon, 7.5; carp, 7.6; gar, 7.6; and hen, 7.6. to 7.7,

or a maximal difference of from 7.3 to 7.7. This variation of 0.4 in pH value, or the buffer value indicated thereby, played no part, nor modified in any way, the production of fat necrosis in the work on the vertebrates here recorded.

Body temperature as a factor in the production of fat necrosis

Three distinct groups of vertebrates depending upon their normal body temperatures were used—first, fish and turtles, poikilothermic animals, second, mammalian types, rats and dogs, and third, avian types, hens and pigeons.

In these experiments, fat necrosis was produced in cold-blooded and warm-blooded groups at several temperatures between 18° and 43°C. Insofar as our data go, there is a suggestion that the necrosis developed more slowly in the cold-blooded animals.

ACTIVE PRINCIPLE CONCERNED IN THE PRODUCTION OF FAT NECROSIS

In 1929, we reported[3] having isolated by accredited chemical procedures, a lipase fraction from: (1) fresh pancreas of the hog; (2) commercial pancreatin, and (3) the dried seeds of: (a) Arachis, the peanut; (b) Helianthus, the common sunflower, and (c) *Ricinus communis*, the castor bean. The lipase fractions from each of these sources have consistently given typical fat necrosis when injected into certain vertebrates.

Regardless of the general source from which this isolated fraction was obtained, and irrespective of which type or species of the above recorded vertebrates was used, fat necrosis was produced in all alike. From a biological standpoint this clearly speaks in favor of the active substance being classed as a ferment or enzyme. Since this enzyme does split fat, reduces ethyl butyrate, and shows no tryptic action on fibrin, it is a lipase. In none of the various vertebrates in which it has been injected has it given rise to any evidence of an anaphylactic reaction. Anatomic or histologic lesions were not found in any pancreas of the entire group injected with this purified lipase, which would indicate that this organ had been damaged, and the pancreatic secretion liberated, thus secondarily producing fat necrosis. That is, fat necrosis was produced by the injected lipase, and not through some damage to the pancreas.

As further, and what is considered conclusive, proof that this active substance is a lipase, we have produced lesions of typical fat necrosis in white rats, by injection of a purely synthetic preparation.

TISSUE CHANGES PRODUCED BY THE ENZYME LIPASE

The lipase fraction does show a different reaction on various forms or combinations of body fats and oils. One phase of this is seen regularly as the production of typical fat necrosis in the fat bodies about the testes or uterine horns, the perirenal fat, and the fat in the omentum and mesentery, following intraperitoneal injections of this substance. The anatomic and histologic findings of fat necrosis as produced by the injections of substances herein recorded as having been used in the experimental production of the lesion have been given in detail in a previous publication.[3]

Another manifestation following injections of the lipase fraction from peanuts (no observations have yet been made following injections of lipase from other sources) is that seen in the maturing eggs within the turtle. These eggs in various stages of developmental maturity show definite gross and histologic changes following injections of these substances. Grossly some of the eggs at different periods of development, but more marked in those having a diameter of 3 to 6 mm. appear partially collapsed, and of discus-shape. Within their covering there appears free oil that is almost colorless surrounding the central yellowish pigmented portion. Histologically, these damaged eggs have an intact surrounding membrane. Immediately within this, there is a zone of non-organized, more or less homogeneous, uniformly deep basic staining material, in which appear free globules of fat. The normal eggs in contrast to these, have a central portion of heavy basic staining round bodies surrounded by lighter neutrophilic staining fine granules. The changes in these eggs are attributed to the action of the injected enzyme, lipase. We have not seen this change under any other condition, nor has it been found recorded in the literature. Similar gross lesions have been observed in eggs within gar injected with the same purified lipase.

Foci of fat necrosis to be differentiated from post-mortem changes

Early in this work it was found that in histologic examination of fat tissue from animals dead for several hours before being necropsied, the sections would show a swelling and cloudiness of the cells, with an acidophilic or basophilic homogeneous staining reaction. This post-mortem fatty change must be differentiated from true fat necrosis. Areas of fat necrosis, small or large, are always surrounded by a margin of undamaged fat cells, and when several hours old, by a zone of leukocytic demarcation. These foci do not appear to extend beyond the normal interlobular septa or strands of fibrous tissue. Attention has previously been called by Wells[5] to this limitation by the septa to areas of fat necrosis. The foci of fat necrosis generally show acicular spaces, fat cells swollen, disrupted, cloudy, and the cytoplasm staining acidophilic or basophilic, but the outstanding differential feature is the presence of a leukocytic cellular reaction surrounding the whole area.

CONCLUSIONS

1. Experimental fat necrosis has been produced in the following vertebrates: (A) Cold-blooded: (1) *Lepisosteus platystomus*, (2) *Cyprinus carpio*, (3) *Macroclamys pseudo-geographica*, (4) *Chrysmes belli cinerea*. (B) Warm-blooded: (1) *Gallina domestica*, (2) *Columba livia*, (3) *Mus decumanus*, (4) *Canis familiaris*.

2. Experimental fat necrosis was produced by injections of: (a) pancreatin; (b) solutions prepared from fresh pancreas of the hog (c) pancreatic secretion from dogs, and (d) the purified extracts from: (1) pancreatin, (2) hog's pancreas, and (3) the seeds of Arachis, Helianthus, and Ricinus.

3. The lipase fractions from these animal and vegetable sources contained the active principle for the production of fat necrosis.

4. The active enzyme fulfilled both biological and chemical criteria for a lipase.

5. Fat necrosis was produced in various animals, in which the body temperatures ranged from 18° to 43°C.

6. The data suggest that the production of fat necrosis proceeds more slowly in the cold-blooded vertebrates.

7. There was no species specificity in the action of this enzyme in producing fat necrosis.

8. Post-mortem changes and pancreatic lesions were eliminated as factors in bringing about the findings recorded as fat necrosis.

9. A change in the contained eggs of gravid fish and turtles was observed.

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EDITORIAL

The Prevalence of Intestinal Amebiasis

Intestinal amebiasis is one of the outstanding diseases, the diagnosis of which must of necessity largely depend upon the knowledge of the clinical pathologist.

From the recent past when amebic infection of the human intestine meant amebic or tropical dysentery to the entire medical profession we have come to the present era in the study of this disease when we have ascertained that dysentery is the relatively uncommon acute phase of this infection. Infection of the human being by *Endamoeba histolytica* is of world-wide distribution and of an incidence which appears to be very high in the general population, according to the observations of many students. Just what the general incidence may be is impossible to state at present but newer studies indicate it to be a remarkably common form of parasitism of the human intestine.

In far the majority of instances the infection does not manifest itself as amebic dysentery, and chronic intestinal amebiasis is being given a larger and larger place and more attention by those who are interested in the study of intestinal disease.

We have believed that we know the nature of the disease produced by this ameba. Its tissue invading and destroying qualities have fixed themselves in our conception of a definite pathogenesis and a characteristic pathological picture. If the infection is as widespread and as prevalent as is indicated by accumulating reports, it becomes necessary to determine whether we really do know the whole story of the activities of amebae in the bowel. What constitutes the state of chronic intestinal amebiasis? Is the ameba capable of living its entire life in the lumen of the intestine with effect on the local tissue? If so, is there any systemic effect of such parasitism? Is there a humoral absorption of a "toxic" product? Or does it invariably invade the intestine wall?

These are problems for the investigation of which many clinical pathologists are favorably situated.

Let it be said at the outset that as a basis for exact and exacting study of amebiasis one should prepare to know the organism. In identifying *Endamoeba histolytica* for the purposes of study in obscure and latent parasitism nothing short of definite recognition of the cyst will probably now suffice. There is too much chance of error by depending entirely upon identification of the trophozoite.

If chronic intestinal amebiasis is as prevalent as commonly indicated and if the ameba is not often simply a lumen dweller, the lesions which characterize it are being overlooked very frequently. The usual post-mortem examination generally carries a rather casual inspection of the intestine, unless it becomes a point of interest from the symptoms presented or because of some readily apparent disease. However, in many places where autopsies are very carefully performed, including a close inspection of the opened intestine, nothing has been discovered to correspond with the conception that amebic intestinal infection is very common. Perhaps the lesions are too small or obscure to be seen even by a careful inspection with the naked eye.

One way in which the problem may be attacked is this: In subjects that have very recently died the large intestine may be tied off in short sections and then each opened and examined separately. The content, particularly that immediately on the mucosa, may be searched by means of fresh wet preparations for amebae. If they are found the section of gut from which they were removed should be studied very thoroughly and minutely, with the hand lens as well as with the unaided eye. Any suspicious spots should be placed in Zenker's fixative, or even if nothing is found, numerous sections of that part should be taken for making histological sections for study.

Such a procedure, as above outlined, might well be instituted with a higher percentage of positive results if routine stool examinations were made on all patients entering large hospitals. Since it is obvious that some of these patients would eventually come to autopsy, it might be expected that a certain number

would be studied sufficiently soon after death so that amebae might be found still alive and hence suitable material for study could be obtained.

It would require a good deal of time to study each case thoroughly, and it would require much care, but it should not be necessary to study any large number of cases before one would have some definite information as to whether *Endamoebia histolytica* may be readily found in the lumen and not in the tissues or that it could be usually demonstrated as a tissue invader in amebiasis. Such a study would have a definite value in the present state of confusion and unsupported hypotheses concerning obscure or latent intestinal amebiasis.

KENNETH M. LYNCH

NEWS AND NOTICES

Tenth Annual Convention of the American Society of Clinical Pathologists

The Committee on Local Arrangements announces the following general program for the meeting to be held in Philadelphia, June 7–9, 1931. The Adelphia Hotel has been selected as convention headquarters. The annual meeting of the Executive Committee of the Society will be held at the Adelphia Hotel on Sunday, June 7. Members of the Executive Committee will receive announcements regarding the place and hour of the meeting. The Scientific Sessions and Scientific Exhibit will be held on Monday, June 8, and Tuesday, June 9, from 9:00 a.m. to 5:00 p.m. at the Philadelphia General Hospital. Programs for the meeting will be mailed in advance to members of the Society. The annual banquet will be held on the evening of June 8 at the Penn Athletic Club. The annual business meeting will be held in the Auditorium of the Philadelphia General Hospital on the evening of June 9.

The tentative program for the Scientific Session is as follows:

Monday Morning, June 8

A discussion of agranulocytic anemia, with report of cases and autopsy findings—H. W. Jones and B. L. Crawford.

The experimental production of agranulocytosis—R. E. Kracke.

Dysplastic granulocytemia—A. M. Weiss and A. A. Goldbloom.

The pathogenesis of acute tuberculous hemoptysis—E. Bogen.

Focal cyclic growth as a factor in the production of nodular goitre—B. Markowitz.

Monday Afternoon, June 8

The starch-iodine reaction in the spinal fluid—B. Gruskin.

The use of the electro-scopometer in routine clinical pathology with new methods—W. G. Exton.

A new modification of the Mallory-Heidenheim differential staining method—J. W. Kernohan.

Experiences in the laboratory diagnosis of tuberculosis with special reference to guinea-pig inoculation—T. B. Magath and W. H. Feldman.
An analysis of 2000 consecutive autopsies—A. O. Brines.
The training of laboratory technicians—R. E. Kracke.

Tuesday Morning, June 9

Active immunization methods against acute, diffuse peritonitis—B. Steinberg.
Experience with bacterial vaccine detoxified with sodium ricinoleate—G. E. Roderick and Ina Maxson.
Standard normals and normal ranges in hematology—F. Boerner.
Physiological properties of the kidney hormone—B. Jablons.
Adenomyoma (endometrial type) of the umbilicus, with report of an additional case—H. Spitz
A case of *Rhinosporidium seeberi* infection—G. S. Graham.
Improved methods in the serum diagnosis of syphilis—H. Engle.

A feature of the program is a symposium on vaccine therapy to be conducted Tuesday afternoon under the auspices of the Committee on Vaccine Therapy. This symposium should be of special interest to members of the Society as well as to general practitioners and it is hoped that there will be a large attendance and that a thorough discussion will result. The following program is announced:

The basic principles of vaccine therapy—John A. Kolmer.
A consideration of the therapeutic and statistical bases for vaccine therapy—N. W. Larkum.
Isolation, selection and preparation of bacteria for vaccines—F. W. Hartman and Edna Jackson.
The use of stock vaccines in respiratory infections in children—Roy P. Forbes.
Bacterial allergy and bacterial densensitization—Warren T. Vaughan.
The therapeutic use of bacteriophage, and its pratical difficulties—Frank B. Lynch, Jr.
Bacterial filtrates in vaccine therapy—John Eiman.
The results of immunization in typhoid fever—S. D. Avery, Major, U. S. A.

Anyone desiring to appear on the program of the Society should communicate with Dr. R. A. Kilduffe before May 15. Those wishing to present exhibits should make requests to Dr. W. S. Thomas, Chairman of the Committee on Exhibits.

Railroad certificates entitling the bearer to half-fare returning

should be secured by members attending the convention. It will be necessary to have these certificates read for the American Medical Association which is in session at the same time, and to have them validated by the proper authorities at the A. M. A. headquarters.

Approved Laboratory Technic

The new book on Approved Laboratory Technic prepared by Dr. John A. Kolmer, Dr. Fred Boerner and Dr. C. Z. Garber with the assistance of a Committee of the American Society of Clinical Pathologists, is now in the hands of the publishers, D. Appleton and Company, with the hope and expectation that it will be published by the time of the meeting in June.

The book is very complete, with adequate illustrations and includes general, clinical pathological, bacteriological, biochemical and serological technic and also a chapter on histological technic by Dr. W. C. MacCarty and Dr. W. L. A. Wellbrock of the Mayo Clinic.

Several years have been spent in its preparation and every method has been revised or passed upon by at least two members of the special Committee of the Society in order to render the technic approved by the A. S. C. P.

An effort has been made to concentrate on single methods for each determination and to give these with sufficient detail for laboratory technicians as well as for assistance to expert pathologists. In many instances, however, alternate methods are included for the purpose of controls or checking wherever it was thought advisable to include them.

The publication of the book is awaited with much interest and with the hope that it will advance the accuracy and status of "clinical pathology" in fulfillment of one of the aims of the A. S. C. P.

Research Committee Notice

Attention is called to the ruling made last year that two or more abstracts of papers to be considered for the Ward Burdick prize shall be submitted to the committee at least one month

before the annual meeting in order that the committee may properly study the contents before the papers are read.

In regard to the hematological registry it is regretted that only two men have sent in reports of cases of blood dyscrasias, with their slides so far this year. It is earnestly hoped that more will send in their material promptly, so that it can be arranged and studied by the committee long before the next meeting. Please send in blood smears, tissue slides, etc., with all cases. As complete a collection as possible is desired for every case. The conditions particularly included this year are: Acute leukemias, agranulocytic angina, blood dyscrasias following arsphenamines, and cases showing blood pictures resembling pernicious anemia, but due to proved etiology.

Comparative records of urine tests for bile by the Huppert-Nakayama method and other methods should be made for future reporting.

Because of the large expense for animals and labor and other factors, the typing of cultures of tubercle bacilli as outlined will have to be deferred until some later year. Meanwhile it would be good policy to develop technique for culturing tubercle bacilli whenever possible, so that typing later could be done more easily.

A. G. FOORD, *Chairman,*
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Openings for clinical pathologists are available in New Jersey and California. Anyone desiring information may write to the Secretary.

BOOK REVIEWS

The Clinical Interpretation of Blood Examinations. By ROBERT A. KILDUFFE. Pp. xvi + 629, 1931, Philadelphia, Lea & Febiger, $6.50.

Dr. Kilduffe is known as an able investigator and abstractor of literature. In this book he has produced a manual that is at once encyclopedic and very practically useful. The book deals not so much with the methods of blood examination but, as the title states, with the clinical interpretations of such tests. The treatment of the various subjects is rather unique and for the student and laboratory man most valuable in that the author gives extremely complete summaries of the important work done in the field with references to the literature.

The outstanding chapters are on blood grouping and on the Wassermann reaction. The first subject he covers from the discovery of blood grouping to the most recent work on its relation to forensic medicine. In the chapter on the Wassermann reaction he brings out forcefully the pitfalls in the interpretation of this important test and the fact that all such tests are "laboratory methods of examination for evidence of reaction to syphilis" and not tests for syphilis.

Because certain subjects are treated twice in the book some duplication arises, particularly in the subjects of hydrogen ion concentration of the blood and sedimentation. The particular style of subdivision in the book which brought this about may be open to question.

As is to be expected in the first edition of such a comprehensive book, certain errors of omission and commission are noticeable. Thus, polycythemia is omitted from the list of causes of increased blood volume and sickle cell anemia is said to occur only in negroes, neither of which are, of course, serious errors.

There are splendid discussions of both the cytology and chemistry of the blood and the numerous references open to the reader

a vast field of literature in these fields. The book is an excellent modern summary of knowledge in the field of clinical laboratory interpretation of hematological examinations.

The Factor of Infection in the Rheumatic State. By ALVIN F. COBURN. Pp. x + 288, 1931, Baltimore, The Williams & Wilkins Company, $6.00.

The author states in the introduction that "the purpose of this study is to give a comprehensive description of the rheumatic state with its many phases." This he has ably put forth in a series of case histories from which he has drawn certain conclusions. To arrive at the picture of this mosaic disease he has examined more than 3,000 rheumatic subjects, more particularly 162 whom he was able to observe over a long period of time. From these studies he has shown that Cheadle's conception of rheumatic fever is essentially correct and that the rheumatic state is distinguishable from other forms of illness, although protean in its manifestations. In order of frequency the most common of these are: Polyarthritis, pancarditis, epixtaxis, muscle pains, pallor, headache occurring with the attacks, cardiac pain, chorea and abdominal symptoms, while skin manifestations and subcutaneous nodules are fairly common.

The author emphasizes the importance of upper respiratory and pulmonary infections as forerunners of the disease. The effect of these and other environmental influences was studied in four widely separated groups of rheumatic people including one colony in Porto Rico. From the study of the New York Hospital group he concludes that there is (1) probably some annual variation, (2) seasonal incidence — the majority of cases appear in the early spring, (3) geographic distribution — almost unknown in the tropics, (4) familial tendency, and (5) influence of the environment of the city. This was studied particularly in immigrants in whom the disease developed for the first time after settling in New York. However, he states that exposure to upper respiratory diseases is more important than other environmental factors.

A large share of the book is devoted to bacterial studies on rheumatic patients and controls. From a large series of carefully

performed blood cultures he concludes, in opposition to Cecil, that bacteremia is not a part of the entity. He brings forth evidence to show the importance of upper respiratory infections as the genesis of the rheumatic state and believes that the important factor is the absorption of toxins from hemolytic streptococci found so frequently in the throats and tonsils of such persons. He definitely recognizes, however, that the physiological state of the individual also plays an important part. As a part of his proof for such a causal relationship to streptococci he details experiments with nucleoproteins obtained from bacteria from the throat and injected into the skin, from which he obtained fairly typical reactions.

It is unfortunate that he fails to recognize that "Streptococcus hemolyticus" really means nothing bacteriologically speaking. No such name appears in Bergey's Manual; many different streptococci produce hemolysis. If he means to incriminate any hemolytic streptococcus he should not use a Latin binomial. Apparently he does not so mean to use the term, yet he does not furnish evidence to support the view that all the organisms he isolated as hemolytic streptococci belong to one species. There is great need to study further the organisms with which he deals.

The book is printed in the usual faultless style of Williams & Wilkins, is well illustrated, and contains many tables and colored plates, one of which illustrating the anaerobic nature of the organism isolated in one case could well have been omitted.

The book will not only take its place on the shelves of serious students of the laboratory side of medicine, but will be useful and appropriate on the desk of the busy practitioner.

The Rôle of the Streptococci in Scarlet Fever. By DAVID THOMSON and ROBERT THOMSON. Annals of the Pickett-Thomson Research Laboratory, Vol. 6, pp. xiii + 470, London, Bailliere, Tindall and Cox, and Baltimore, Williams & Wilkins Company.

This is an extensive and valuable collection of the literature which includes 1,400 papers. The authors point out in the preface that this literature represents 1,000 years of work. They conclude that "the weight of evidence shows scarlet fever to be

due to a specific streptococcus, the *Streptococcus scarlatinae.*" In the summary are listed fifteen types of experimental evidence to support this contention. Such evidence is based upon (1) cultural differences, (2) fermentation tests, (3) agglutination tests, (4) opsonic tests, (5) precipitin tests, (6) specificity of toxin, (7) production of rash by toxin, (8) production of rash by vaccine, (9) Schultz-Charlton phenomenon, (10) curative action of antiserum, (11) production of short immunity by antiserum, (12) immunization by toxin and vaccine, (13) experimental production of scarlet fever, (14) milk borne epidemics, and (15) contraction of scarlet fever in the laboratory.

A more conservative opinion after examination of the literature on these various points would be that scarlet fever is due to a hemolytic streptococcus, but proof as to its specificity is far from complete. If, for example, one were to examine the results of fermentation tests cited by the authors to differentiate the streptococcus of scarlet fever from other types of hemolytic streptococci, one would find that of fourteen reactions eight are variable. While it may be true that the streptococci from scarlet fever will give a certain set of reactions more frequently than streptococci from other diseases, yet the notable exceptions to be found in the fermentation tests, and in most of the other tests set up as criteria of specificity, remain to disturb the critically-minded person and serve as a commentary on the difficulty of the problem.

LUTHER THOMPSON.